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(54) Title: NOVEL BAG PROTEINS AND NUCLEIC ACID MOLECULES ENCODING THEM (57) Abstract The present invention provides a family of BAG-1 related proteins from humans (BAG-1L, BAG-1, BAG-2, BAG-3, BAG-4 and BAG-5), the invertebrate <i>C. elegans</i> (BAG-1, BAG-2) and the fission yeast <i>S. pombe</i> (BAG-1A, BAG-1B) and the nucleic acid molecules that encode them.		

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NOVEL BAG PROTEINS AND NUCLEIC ACID MOLECULES ENCODING THEM

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5 This invention was made with government support
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BACKGROUND OF THE INVENTION

10 FIELD OF THE INVENTION

This invention relates generally to the fields of molecular biology and molecular medicine and more specifically to a novel family of proteins that can regulate protein folding. The functions of these proteins are potentially diverse, including promoting tumor cell growth and metastasis.

BACKGROUND INFORMATION

The Hsc70/Hsp70-family of molecular chaperones participate in protein folding reactions, controlling protein bioactivity, degradation, complex assembly/disassembly, and translocation across membranes. These proteins interact with hydrophobic regions within target proteins via a carboxyl (C)-terminal peptide binding domain, with substrate binding and release being controlled by the N-terminal ATP-binding domain of Hsc70/Hsp70. Hsc70/Hsp70-assisted folding reactions are accomplished by repeated cycles of peptide binding, refolding, and release,

which are coupled to ATP hydrolysis by the ATP-binding domain (ATPase) of Hsc70/Hsp70 and by subsequent nucleotide exchange. The chaperone activity of mammalian Hsc70/Hsp70 is regulated by partner proteins that either modulate the peptide binding cycle or that target the actions of these chaperones to specific proteins and subcellular compartments. DnaJ-family proteins (Hdj-1/Hsp40; Hdj-2; Hdj-3) stimulate the ATPase activity of Hsc70/Hsp70, resulting in the ADP-bound state which binds tightly to peptide substrates. The Hip protein collaborates with Hsc70/Hsp70 and DnaJ homologues in stimulating ATP hydrolysis, and thus also stabilize Hsc70/Hsp70 complexes with substrate polypeptides, whereas the Hop protein may provide co-chaperone functions through interactions with the C-terminal peptide binding domain.

The Bcl-2 associated athanogene-1 (bag-1) is named from the Greek word *athanos*, which refers to anti-cell death. BAG-1 was previously referred to as Bcl-2-associated protein-1 (BAP-1) in U.S. Patent No. 5,539,094 issued July 23, 1996, which is incorporated herein by reference. In this earlier patent, BAG-1 is described as a portion of the human BAG-1 protein, absent the N-terminal amino acids 1 to 85. In addition, a human protein essentially identical to human BAG-1 was described by Zeiner and Gehring, (*Proc. Natl. Acad. Sci., USA* **92**:11465-11469 (1995)). Subsequent to the issuance of U.S. Patent 5,539,094 the N-terminal amino acid sequence from 1 to 85 of human BAG-1 was reported.

BAG-1 and its longer isoforms BAG-1M (Rap46) and BAG-1L are recently described Hsc70/Hsp70-regulating proteins. BAG-1 competes with Hip for binding to the Hsc70/Hsp70 ATPase domain and promotes substrate release. BAG-1 also reportedly stimulates Hsc70-mediated ATP

hydrolysis by accelerating ADP/ATP exchange, analogous to the prokaryotic GrpE nucleotide exchange protein of the bacterial Hsc70 homologue, DnaK. Gene transfection studies indicate that BAG-1 proteins can influence a wide variety of cellular phenotypes through their interactions with Hsc70/Hsp70, including increasing resistance to apoptosis, promoting cell proliferation, enhancing tumor cell migration and metastasis, and altering transcriptional activity of steroid hormone receptors.

Despite the notable progress in the art, there remains an unmet need for the further identification and isolation of additional homologous BAG protein species, and the nucleic acid molecules and/or nucleotide sequences that encode them. Such species would provide additional means by which the identity and composition of the BAG domain, that is, the portion of the protein that is influencing or modulating protein folding, could be identified. In addition, such species would be useful for identifying agents that modulate apoptosis as candidates for therapeutic agents, in particular, anticancer agents. The present invention satisfies these need, as well as providing substantial related advantages.

SUMMARY OF THE INVENTION

The present invention provides a family of BAG-1 related proteins from humans [BAG-1L (SEQ ID NO:2), BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO: 4), BAG-3 (SEQ ID NO:6) and (SEQ ID NO:20), BAG-4 (SEQ ID NO:8) and (SEQ ID NO:22) and BAG-5 (SEQ ID NO:10) and (SEQ ID NO:24)] , the invertebrate *C.elegans* [BAG-1 (SEQ ID NO:12), BAG-2 (SEQ ID NO:14)] and the fission yeast *S.pombe* [BAG-1A (SEQ ID NO:16), BAG-1B (SEQ ID NO:18)] and the nucleic acid molecules that encode them.

Another aspect of the present invention provides an amino acid sequence present in the family of BAG-1 related proteins, that modulates Hsc70/Hsp70 chaperone activity, that is, the BAG domain.

5 Another aspect of the present invention provides novel polypeptide and nucleic acid compositions and methods useful in modulating Hsc70/Hsp70 chaperone activity.

Another aspect of the present invention is directed to methods for detecting agents that modulate the
10 binding of the BAG family of proteins, such as BAG-1 (beginning at residue 116 of SEQ ID NO:2), and related proteins with the Hsc70/Hsp70 Family of proteins or with other proteins that may interact with the BAG-Family proteins.

15 Still another aspect of the present invention is directed to methods for detecting agents that induce the dissociation of a bound complex formed by the association of BAG-Family proteins with Hsc70/Hsp70 Family molecule chaperones or other proteins.

20 **BRIEF DESCRIPTION OF THE DRAWINGS**

Figure 1 shows the full length cDNA sequence for human BAG-1 (SEQ ID NO:1) protein with the corresponding amino acid sequence (SEQ ID NO:2). Within the full length sequence are included the overlapping sub-sequences of
25 BAG-1 (beginning at nucleotide 391), BAG-1M [beginning at nucleotide 260 of (SEQ ID NO:2)], and BAG-1L [beginning at nucleotide 46 of (SEQ ID NO:2)].

Figures 2A and 2B combined shows the full length cDNA sequence (SEQ ID NO:3) aligned with the corresponding amino acid residues for human BAG-2 protein (SEQ ID NO:4).

Figure 3 shows a cDNA sequence (SEQ ID NO:5)
5 aligned with the corresponding amino acid residues for human BAG-3 protein (SEQ ID NO:6).

Figure 4 shows the a cDNA sequence (SEQ ID NO:7) aligned with the corresponding amino acid residues for human BAG-4 protein (SEQ ID NO:8).

10 Figure 5 shows a cDNA sequence (SEQ ID NO:9) aligned with the corresponding amino acid residues for human BAG-5 protein (SEQ ID NO:10).

Figure 6A shows the full length cDNA sequence for *C. elegans* BAG-1 protein (SEQ ID NO:11).

15 Figure 6B shows the 210 amino acid sequence for *C. elegans* BAG-1 protein (SEQ ID NO:12).

Figure 7A shows the full length cDNA sequence for *C. elegans* BAG-2 protein (SEQ ID NO:13).

20 Figure 7B shows the 458 amino acid sequence for *C. elegans* BAG-2 protein (SEQ ID NO:14).

Figure 8A shows the full length cDNA sequence for *S. pombe* BAG-1A protein (SEQ ID NO:15).

Figure 8B shows the 195 amino acid sequence for *S. pombe* BAG-1A protein (SEQ ID NO:16).

Figure 9A shows the full length cDNA sequence for *S. pombe* BAG-1B protein (SEQ ID NO:17).

Figure 9B shows the 206 amino acid sequence for *S. pombe* BAG-1B protein (SEQ ID NO:18).

5 Figure 10 shows the topologies of the BAG-family proteins; human BAG proteins, BAG-1 (SEQ ID NO:2), BAG-2 (SEQ ID NO:4), BAG-3 (SEQ ID NO:6), BAG-4 (SEQ ID NO:8), BAG-5 (SEQ ID NO:10); *S.pombe* BAG-1A (SEQ ID NO:16) and BAG-1B (SEQ ID NO:18); and *C. elegans* BAG-1 (SEQ ID NO:12) and BAG-2 (SEQ ID NO:14). (A) The relative positions of the BAG domains are shown in black, ubiquitin-like regions are represented in gray, WW domain are represented in strips. Nucleoplasmin-like nuclear localization sequence are also shown. (B) The amino acid sequences of the BAG domain for human BAG-1 (SEQ ID NO:2), BAG-2 (SEQ ID NO:4), BAG-3 (SEQ ID NO:6), BAG-4 (SEQ ID NO:8), BAG-5 (SEQ ID NO:10), *S.pombe* BAG-1A (SEQ ID NO:16) and BAG-1B (SEQ ID NO:18), and *C. elegans* BAG-1 (SEQ ID NO:12) and BAG-2 (SEQ ID NO:14) are aligned demonstrating their homology. Black and gray shading represent identical and similar amino acids, respectively.

Figure 11 shows assays demonstrating the interaction of BAG-family proteins with Hsc70/ATPase. (A) Two-hybrid assays using yeast expressing the indicated fusion proteins. Blue color indicates a positive interaction, resulting in activation of the *lacZ* reporter gene. (B) *In vitro* protein assays using GST-fusion proteins and ³⁵S-labeled *in vitro* translated proteins. (C) Co-immunoprecipitation assays using anti-Flag or IgG1 control antibodies and lysates from 293T cells expressing Flag-tagged BAG-1 (beginning at residue 116 of SEQ ID

NO:2), BAG-2 (SEQ ID NO:4), BAG-3 (SEQ ID NO:6), Daxx, or Apaf-1.

Figure 12 shows surface plasmon resonance analysis of BAG-family protein interactions with Hsc70/ATPase. (A) SDS-PAGE analysis of purified recombinant proteins. (B) Representative SPR results of biosensor chips containing immobilized BAG proteins with and without maximally bound Hsc70/ATPase.

Figure 13 shows representative SPR results for biosensor chips containing immobilized BAG-1 (beginning at residue 116 at SEQ ID NO:2), BAG-1(Δ C), BAG-2 (SEQ ID NO:4), or BAG-3 (SEQ ID NO:6) proteins. Hsc70/ATPase was flowed over the chips (arrow/left) until maximal binding was reached (response units), then flow was continued without Hsc70/ATPase (arrow/right). For BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6), Hsc70 was injected at 0.0175, 0.035, 0.07, 0.14, and 0.28 μ M.

Figure 14 shows BAG-family protein modulation of Hsc70 chaperone activity. (A) Protein refolding assay of chemically-denatured luciferase by Hsc70 plus DnaJ in the absence or presence of BAG and BAG-mutant proteins. (B) Concentration-dependent inhibition of Hsc70-mediated protein refolding by BAG-family proteins [BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), BAG-3 (SEQ ID NO:6)] but not by BAG-mutant (BAG-1 (Δ C)). (C) Hsc70/Hsp40-mediated refolding of heat-denatured luciferase was assayed in the presence of (black bars) or absence of (striped bars) of 1.8 μ M Hip, with (lanes 3-10) or without (lanes 1,2) various BAG-family proteins (1.8 μ M) as indicated (mean \pm SE; n=3). A control (CNTL) is shown (lane 1) in which Hsc70 was replaced with an equivalent amount of BSA.

Figure 15A shows an expanded cDNA sequence for human BAG-3 protein (SEQ ID NO:19).

Figure 15B shows the corresponding amino acid residues for the human BAG-3 protein (SEQ ID NO:20) of
5 Figure 15A.

Figure 15C shows the expanded cDNA sequence (SEQ ID NO:19) aligned with the corresponding amino acid residues for human BAG-3 protein of Figure 15A (SEQ ID NO:20).

10 Figure 16A shows an expanded cDNA sequence for human BAG-4 protein (SEQ ID NO:21).

Figure 16B shows the corresponding amino acid residues for the human BAG-4 protein of Figure 16A (SEQ ID NO:22).

15 Figure 16C shows the expanded cDNA sequence (SEQ ID NO:21) aligned with the corresponding amino acid residues for human BAG-4 protein of Figure 16A (SEQ ID NO:22).

Figure 17A shows an expanded cDNA sequence for
20 human BAG-5 protein (SEQ ID NO:23).

Figure 17B shows the corresponding amino acid residues for the human BAG-5 protein of Figure 17A (SEQ ID NO:24).

Figure 17C shows the expanded cDNA sequence (SEQ
25 ID NO:23) aligned with the corresponding amino acid residues for human BAG-5 protein of Figure 17A (SEQ ID NO:24).

Figure 18 shows the topologies of the BAG-family proteins; human BAG proteins, BAG-1 (SEQ ID NO:2), BAG-2 (SEQ ID NO:4), expanded BAG-3 (SEQ ID NO:20), expanded BAG-4 (SEQ ID NO:22), expanded BAG-5 (SEQ ID NO:24);
5 *S.pombe* BAG-1A (SEQ ID NO:16) and BAG-1B (SEQ ID NO:18); and *C. elegans* BAG-1 (SEQ ID NO:12) and BAG-2 (SEQ ID NO:14). The relative positions of the BAG domains are shown in black, ubiquitin-like regions are represented in gray, WW domain are represented in strips. Nucleoplasmin-like
10 nuclear localization sequence are also shown.

Definitions

The term "apoptosis", as used herein, refers to the process of programmed cell death, although not all programmed cell deaths occur through apoptosis, as used
15 herein, "apoptosis" and "programmed cell death" are used interchangeably.

The term "tumor cell proliferation", as used herein refers to the ability of tumor cells to grow and thus expand a tumor mass.

20 The term "cell migration", as used herein refers to the role cell motility plays in the invasion and potentially metastasis by tumor cells.

The term "metastasis", as used herein refers to the spread of a disease process from one part of the body to another, as in the appearance of neoplasms in parts of
25 the body remote from the site of the primary tumor; results in dissemination of tumor cells by the lymphatics or blood vessels or by direct extension through serious cavitites or subarachnoid or other spaces.

The term "steroid hormone receptor function", as used herein refers to physiological, cellular and molecular functioning of receptors sites that bind with steroid hormones.

5 The term "substantially purified", as used herein, refers to nucleic acid or amino acid sequence that are removed from their natural environment, isolated or separated, and are at least 60% free, preferably 75% free, and most preferably 90% free from other components with
10 which they are naturally associated.

"Nucleic acid molecule" as used herein refers to an oligonucleotide, nucleotide, or polynucleotide, and fragments or portions thereof, and to DNA or RNA of genomic or synthetic origin which may be single or double stranded,
15 and represent the sense or antisense strand.

"Hybridization", as used herein, refers to any process by which a strand of nucleic acid binds with a complementary strand through base pairing.

The terms "complementary" or "complementarity",
20 as used herein, refer to the natural binding of polynucleotides under permissive salt and temperature conditions by base-pairing. For example, the sequence "A-G-T binds to the complementary sequence "T-C-A".

The term "homology", as used herein, refers to a
25 degree of complementarity. There may be partial homology or complete homology (i.e., identity). A partially complementary sequence is one that at least partially inhibits an identical sequence from hybridizing to a target nucleic acid and is referred to using the functional term
30 "substantially homologous." The inhibition of

hybridization of the completely complementary sequence to the target sequence may be examined using a hybridization assay (Southern or northern blot, solution hybridization and the like) under conditions of low stringency. A substantially homologous sequence or probe will compete for and inhibit the binding (i.e., the hybridization) of a completely homologous sequence or probe to the target sequence under conditions of low stringency.

The term "antisense", as used herein, refers to nucleotide sequences which are complementary to a specific DNA or RNA sequence. The term "antisense strand" is used in reference to a nucleic acid strand that is complementary to the "sense" strand. Antisense molecules may be produced by any method, including synthesis by ligating the gene(s) of interest in a reverse orientation to a viral promoter which permits the synthesis of a complementary strand. Once introduced into a cell, this transcribed strand combines with natural sequences produced by the cell to form duplexes. These duplexes then block either the further transcription or translation. In this manner, mutant phenotypes may be generated. The designation "negative" is sometimes used in reference to the antisense, and "positive" is sometimes used in reference to the sense strand.

"Amino acid sequence" as used herein refers to an oligopeptide, peptide, polypeptide, or protein sequence, and fragments or portions thereof, and to naturally occurring or synthetic molecules. Where "amino acid sequence" is recited herein this term excludes an amino acid sequence of a naturally occurring protein. "Amino acid sequence", "polypeptide" or "protein" are not meant to limit the amino acid sequence to the complete, native amino acid sequence associated with the recited protein molecule.

The term "functional fragments" or "fragments", as used herein, with regard to a protein refers to portions of that protein that are capable of exhibiting or carrying out the activity exhibited by the protein as a whole. The portions may range in size from three amino acid residues to the entire amino acid sequence minus one amino acid. For example, a protein "comprising at least a functional fragment of the amino acid sequence of SEQ ID NO:1", encompasses the full-length of the protein of SEQ ID NO:1 and portions thereof.

A "derivative" of a BAG protein, as used herein, refers to an amino acid sequence that is altered by one or more amino acids. The derivative may have "conservative" changes, wherein a substituted amino acid has similar structural or chemical properties, e.g., substitution of an apolar amino acid with another apolar amino acid (such as replacement of leucine with isoleucine). The derivative may also have "nonconservative" changes, wherein a substituted amino acid has different but sufficiently similar structural or chemical properties that permits such a substitution without adversely effecting the desired biological activity, e.g., replacement of an amino acid with an uncharged polar R group with an amino acid with an apolar R group (such as replacement of glycine with tryptophan), or alternatively replacement of an amino acid with a charged R group with an amino acid with an uncharged Polar R group (such as replacement of lysine with asparagine).

Amino Acids - Apolar R Groups

	Amino Acid	Radical	Abbreviations	
			3-Letter	1-Letter
	alanine	methyl	ala	A
	valine	2-propyl	aal	V
5	leucine	2-methylpropyl	leu	L
	isoleucine	2-butyl	ile	I
	proline	propyl* - cyclized	pro	P
	phenylalanine	benzyl	phe	F
	tryptophan	3-indolylmethl	tyr	W
10	methionine	methylthioethyl	met	M

Amino Acids - Uncharged Polar R Groups

	Amino Acid	Radical	Abbreviations	
			3-Letter	1-Letter
	glycine	H	gly	G
	serine	hydroxymethyl	ser	S
15	threonine	1-hydroxyethyl	thr	T
	cysteine	thiolmethyl	cys	C
	tyrosine	4-hydroxyphenylmethyl	tyr	Y
	asparagine	aminocarbonylmethyl	asn	N
	glutamine	aminocarbonylethyl	gln	Q

20 Amino Acids - Charged R Groups

	Amino Acid	Radical	Abbreviations	
			3-Letter	1-Letter
	aspartic acid	carboxymethyl	asp	D
	glutamic acid	carboxyethyl	glu	E
	lysine	4-aminobutyl	lys	K
25	arginine	3-guanylpropyl	arg	R
	histidine	4-imidazoylethyl	his	H

Similar minor modifications may also include amino acids deletions or insertions or both. Guidance in determining which amino acid residues may be modified as indicated above without abolishing the desired biological
5 functionality may be determined using computer programs well known in the art, for example, DNASTAR software. In addition, the derivative may also result from chemical modifications to the encoded polypeptide, including but not limited to the following, replacement of hydrogen by an
10 alkyl, acyl, or amino group; esterification of a carboxyl group with a suitable alkyl or aryl moiety; alkylation of a hydroxyl group to form an ether derivative. Further a derivative may also result from the substitution of a L-configuration amino acid with its corresponding D-
15 configuration counterpart.

The term "mimetic", as used herein, refers to a molecule, the structure of which is developed from knowledge of the structure of a protein/polypeptide or portions thereof (such as BAG-1) and, as such, is able to
20 effect some or all of the actions of BAG-1 protein.

"Peptide nucleic acid", as used herein, refers to a molecule which comprises an oligomer to which an amino acid residue, such as lysine, and an amino group have been added. These small molecules, also designated anti-gene
25 agents, stop transcript elongation by binding to their complementary strand of nucleic acid (Nielsen, P.E. et al., *Anticancer Drug Des.* 8:53-63 (1993)).

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a family of BAG-1
30 related proteins from humans [BAG-1L (SEQ ID NO:2), BAG-1S beginning at residue 116 of SEQ ID NO:2, BAG-2 (SEQ ID

NO:4), BAG-3 (SEQ ID NO:6) and (SEQ ID NO:20), BAG-4 (SEQ ID NO: 8) and (SEQ ID NO:22) and BAG-5 (SEQ ID NO:10) and (SEQ ID NO:24)], the invertebrate *C.elegans* [BAG-1 (SEQ ID NO:12), BAG-2 (SEQ ID NO:14)] and the fission yeast *S.pombe* 5 [BAG-1A (SEQ ID NO:16), BAG-1B (SEQ ID NO:18)], specifically the full length amino acid sequences comprising human BAG-1L (SEQ ID NO:2), BAG-1 (beginning at residue 116 of SEQ ID NO:2), and BAG-2 (SEQ ID NO:4) *C.elegans* BAG-1 (SEQ ID NO:12), and BAG-2 (SEQ ID NO:14), and 10 *S.pombe* BAG-1A (SEQ ID NO:16) and BAG-1B (SEQ ID NO:18); and partial sequences comprising human BAG-3 (SEQ ID NO: 6) and (SEQ ID NO:20), BAG-4 (SEQ ID NO:8) and (SEQ ID NO:22), and BAG-5 (SEQ ID NO:10) and (SEQ ID NO:24) and functional fragments thereof. In particular, the invention provides 15 the amino acid sequences comprising human BAG-2 (SEQ ID NO:4), BAG-3 (SEQ ID NO:6) and (SEQ ID NO:20), BAG-4 (SEQ ID NO:8) and (SEQ ID NO:22), and BAG-5 (SEQ ID NO:10) and (SEQ ID NO:24) proteins.

Another aspect of the present invention provides 20 the nucleic molecule and nucleotide sequences that encode the family of BAG-1 related proteins from humans [BAG-1 (SEQ ID NO:1), BAG-2 (SEQ ID NO:3), BAG-3 (SEQ ID NO:5) and (SEQ ID NO:19), BAG-4 (SEQ ID NO:7) and (SEQ ID NO:21) and BAG-5 (SEQ ID NO:9) and (SEQ ID NO:23)], the invertebrate 25 *C.elegans* [BAG-1 (SEQ ID NO:11), BAG-2 (SEQ ID NO:13)] and the fission yeast *S.pombe* [BAG-1A (SEQ ID NO:15), BAG-1B (SEQ ID NO:17)].

BAG-1L (SEQ ID NO:2) is a multifunctional protein that blocks apoptosis, promotes tumor cell metastasis, and 30 contributes to factor-independent and p53-resistant cell growth. BAG-1L (SEQ ID NO:2) interacts with several types of proteins, including Bcl-2, some tyrosine kinase growth

factor receptors, steroid hormone receptors, and the p53-induced cell cycle regulator Siah-1A.

BAG-1 is a regulator of Hsc70/Hsp70 family molecular chaperones. A carboxyl-terminal domain in this protein binds tightly to the ATPase domains of Hsc70 and Hsp70 ($K_D = 1$ nM) (Zeiner, M., Gebauer, M., and Gehring, U., *EMBO J.* **16**: 5483-5490, (1997)). BAG-1 modulates the activity of these molecular chaperones, acting as an apparent functional antagonist of the Hsp70/Hsc70-associated protein Hip (3-5) (Höhfeld, J. and Jentsch, S., *EMBO J.* **16**: 6209-6216, (1997); Takayama, S., Bimston, D. N., Matsuzawa, S., Freeman, B. C., Aime-Sempe, C., Xie, Z., Morimoto, R. J., and Reed, J. C., *EMBO J.* **16**: 4887-96, (1997); Zeiner, M., Gebauer, M., and Gehring, U., *EMBO J.* **16**: 5483-5490, (1997)). In general, protein refolding is accomplished by Hsp70/Hsc70 through repeated cycles of target peptide binding and release, coupled to ATP hydrolysis (Ellis, R., *Curr Biol.* **7**: R531-R533, (1997)). BAG-1 appears to promote substrate release, whereas Hip stabilizes Hsp70/Hsc70 complex formation with target peptides (Höhfeld, J., Minami, Y., and Hartl, F.-U., *Cell.* **83**: 589-598, (1995)). Since each substrate interaction with Hsc70/Hsp70 is unique in terms of the optimal length of time the protein target should remain complexed with Hsc70/Hsp70 for achieving new conformations, the net effect of BAG-1 can be either enhancement or inhibition of the refolding reaction.

The 70kd heat shock family proteins (Hsp70/Hsc70) are essential to a variety of cellular processes and have been implicated in cancer, yet it is unclear how these proteins are regulated *in vivo*. A variety of co-chaperones have been identified which may target Hsp70/Hsc70 to different subcellular compartments or promote their

interactions with specific protein or protein complexes. BAG-1 appears to represent a novel Hsp70/Hsc70 regulator which differs functionally from all other mammalian co-chaperones identified to date, such as members of the
5 DnaJ-, Hip-, Hop-, and cyclophilin-families of proteins.

Another aspect of the present invention provides the amino acid sequence of a binding domain of about 40 to 55 amino acids that bind the a Hsc70/Hsp70 ATPase domain. The BAG domain is situated near the C-terminus, and the
10 ubiquitin-like domains are situated near the N-terminus.

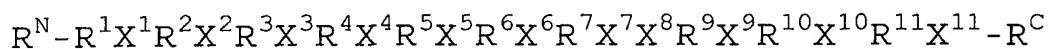
The BAG family of proteins of the present invention contain a common conserved C-terminal domain (the "BAG" domain) that facilitates binding to the ATPase domain of Hsp70/Hsc70. The carboxyl-terminal domain of BAG-1
15 binds to the ATPase domain of Hsc70/Hsp70 and regulates its chaperone function by acting as a ADP-ATP exchange factor. Other domains of BAG-1 mediate interactions with proteins such as Bcl-2 and retinoic acid receptors (RARs), allowing BAG-1 to target Hsc70/Hsp70 to other proteins, presumably
20 modulating their function by changing their conformations.

Human BAG-1 was previously shown to inhibit Hsc70/Hsp70 dependent refolding of denatured protein substrates *in vitro* (S. Takayama, et al., *EMBO J* **16**, 4887-96 (1997); M. Zeiner, M. Gebauer, U. Gehring, *EMBO J.* **16**,
25 5483-5490 (1997); and J. Höhfeld, S. Jentsch, *EMBO J.* **16**, 6209-6216 (1997)). In Example III, Part A the effects of recombinant human BAG-1, BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) were compared using *in vitro* protein refolding assays similar to those employed previously for assessing
30 BAG-1. The study showed that addition of equimolar amounts of each of the recombinant proteins to Hsc70 resulted in significant inhibition of luciferase refolding, with BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) showing somewhat

greater inhibitor activity than BAG-1 (Figure 4A). In a separate luciferase folding study BAG-1, BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) once again displayed inhibition of luciferase refolding, however in this study
 5 varying amounts of BAG-1, BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) were added relative to Hsc70 which resulting in concentration-dependent inhibition of Hsc70 chaperone activity, i.e., luciferase folding (Example III Part A). Additional follow on studies using the same experimental
 10 protocols as the previous studies, as taught in Example IIA, have shown that BAG-4 (SEQ ID NO:22) also undergoes association with Hsc70/ATPase.

Yet another aspect of the present invention provides a nucleotide sequence having at least about 15
 15 nucleotides and, generally, about 25 nucleotides, preferably about 35 nucleotides, more preferably about 45 nucleotides, and most preferably about 55 nucleotides that can hybridize or is complementary under relatively stringent conditions to a portion of the nucleic acid
 20 sequences shown in Figures 1-9 and Figures 15-17, in particular the BAG domain as shown in in Figure 1B, e.g., nucleotides 552-593 of human BAG-3, or nucleotides 167-221 of human BAG-4.

Yet another aspect of the present invention
 25 provides a compound of the formula,



wherein,

R^N is a group of 1 to 552 independently selected amino acids;

30 R^1 is a group of 3 independently selected amino acids;

X^1 is an amino acid with a charged or uncharged R group, such as aspartic acid, glutamic acid, asparagine, or glutamine;

R^2 is a group of 7 independently selected amino acids;

X^2 is an amino acid with a charged R group, such as glutamic acid;

R^3 is a group of 5 independently selected amino acids;

X^3 is an amino acid with an apolar R group, such as leucine, methionine, or isoleucine;

R^4 is a group of 3 independently selected amino acids;

X^4 is an amino acid with charged R group, such as aspartic acid or glutamine acid;

R^5 is a single independently selected amino acid;

X^5 is an amino acid with apolar or uncharged R group, such as leucine, valine, methionine, alanine or threonine;

R^6 is a group of 15 independently selected amino acids;

X^6 is an amino acid with a charged or uncharged R group, such as arginine, lysine, glutamine or aspartic acid;

R^7 is a group of 2 independently selected amino acids;

X^7 is an amino acid with a charged R group, such as arginine;

X^8 is an amino acid with a charged R group, such as arginine or lysine;

R^9 is a group of 2 independently selected amino acids;

X^9 is an amino acid with an apolar R group, such as valine;

R^{10} is a group of 3 independently selected amino acids;

X¹⁰ is an amino acid with an uncharged R group, such as glutamine;

R¹¹ is a group of 2 independently selected amino acids;

5 X¹¹ is an amino acid with an apolar R group, such as leucine; and

R^C is a group of 1 to 100 independently selected amino acids.

A nucleotide sequence of at least about 15
10 nucleotides and, generally, about 25 nucleotides, preferably about 35 nucleotides, more preferably about 45 nucleotides, and most preferably about 55 nucleotides can be useful, for example, as a primer for the polymerase chain reaction (PCR) or other similar reaction mediated by
15 a polymerase such as a DNA or RNA polymerase (see PCR Protocols: A guide to methods and applications, ed. Innis et al. (Academic Press, Inc., 1990), which is incorporated herein by reference; see, for example, pages 40-41). In addition, such a nucleotide sequence of the invention can
20 be useful as a probe in a hybridization reaction such as Southern or northern blot analysis or in a binding assay such as a gel shift assay.

A nucleotide sequence of the invention can be particularly useful as an antisense molecule, which can be
25 DNA or RNA and can be targeted to all or a portion of the 5'-untranslated region or of the 5'-translated region of a bag-1 nucleic acid sequence in a cell. For example, an antisense molecule can be directed to at least a portion of the sequence shown as the BAG domain in Figure 1A, e.g.,
30 nucleotides 272-319 of human BAG-1L (SEQ ID NO:1), or nucleotides 79-147 of human BAG-5 (SEQ ID NO:9). Since the 5'-region of a nucleic acid contains elements involved in the control of expression of an encoded protein, an antisense molecule directed to the 5'-region of a nucleic

acid molecule can affect the levels of protein expressed in a cell.

A nucleotide sequence of the invention also can be useful as a probe to identify a genetic defect due a
5 mutation of a gene encoding a BAG protein in a cell. Such a genetic defect can lead to aberrant expression of a BAG protein in the cell or to expression of an aberrant BAG protein, which does not properly associate with a Bcl-2-related protein or Hsc70/Hsp70 protein in the cell. As a
10 result, a genetic defect in a gene encoding, for example, human BAG-1 can result in a pathology characterized by increased or decreased levels in protein folding.

Further a nucleotide compound or composition as taught in the present invention can be synthesized using
15 routine methods or can be purchased from a commercial source. In addition, a population of such nucleotide sequences can be prepared by restriction endonuclease or mild DNase digestion of a nucleic acid molecule that contains nucleotides as shown in the nucleotide sequences
20 shown in Figures 1-9 and Figures 15-17 that encodes the amino acids sequences also shown in Figures 1-9 and Figures 15-17. Methods for preparing and using such nucleotide sequences, for example, as hybridization probes to screen a library for homologous nucleic acid molecules
25 are well known in the art (see, for example, Sambrook et al., *Molecular Cloning: A laboratory manual* (Cold Spring Harbor Laboratory Press 1989); Ausubel et al., *Current Protocols in Molecular Biology* (Green Publ., NY 1989), each of which is incorporated herein by reference).

30 A particular nucleotide sequence can be designed based, for example, on a comparison of the nucleic acid molecules encoding any one of the BAG family proteins, as shown in Figures 1-9 and Figures 15-17, with another in the family. Such a comparison allows, for example, the

preparation of a nucleotide sequence that will hybridize to a conserved region present in both nucleic acid molecules, thus providing a means to identify homologous nucleic acid molecules present in other cell types or other organisms.

5 In addition, such a comparison allows the preparation of a nucleotide sequence that will hybridize to a unique region of any of the BAG family nucleotide sequences, such as those corresponding to the BAG domain, thus allowing identification of other proteins sharing this motif. In

10 this regard, it is recognized that, while the human BAG-3 proteins shown as Figures 3 and 20, and human BAG-5 proteins shown as Figures 5 and 24, are only partial sequences, a variant human BAG-3 or BAG-5 produced, for example, by alternative splicing can exist and can be

15 identified using an appropriately designed nucleotide sequence of the invention as a probe. Such useful probes readily can be identified by inspection of the sequences shown in the disclosed Figures by a comparison of the encoding nucleotide sequences.

20 If desired, a nucleotide sequence of the invention can incorporate a detectable moiety such as a radiolabel, a fluorochrome, a ferromagnetic substance, a luminescent tag or a detectable binding agent such as biotin. These and other detectable moieties and methods of

25 incorporating such moieties into a nucleotide sequence are well known in the art and are commercially available. A population of labelled nucleotide sequences can be prepared, for example, by nick translation of a nucleic acid molecule of the invention (Sambrook et al., *supra*,

30 1989; Ausubel et al., *supra*, 1989).

One skilled in the art would know that a method involving hybridization of a nucleotide sequence of the invention can require that hybridization be performed under relatively stringent conditions such that nonspecific

35 background hybridization is minimized. Such hybridization

conditions can be determined empirically or can be estimated based, for example, on the relative GC content of a sequence and the number of mismatches, if known, between the probe and the target sequence (see, for example, 5 Sambrook et al., *supra*, 1989).

The invention further provides antibodies specific for human BAG family protein. As used herein, the term "antibody" includes polyclonal and monoclonal antibodies, as well as polypeptide fragments of antibodies 10 that retain a specific binding activity for human BAG-1 of at least about $1 \times 10^5 \text{ M}^{-1}$. One skilled in the art would know that anti-BAG-1 antibody fragments such as Fab, F(ab')_2 and Fv fragments can retain specific binding activity for human BAG-1 (beginning at residue 116 of SEQ ID NO:2) and, 15 thus, are included within the definition of an antibody. In addition, the term "antibody" as used herein includes naturally occurring antibodies as well as non-naturally occurring antibodies and fragments that retain binding activity such as chimeric antibodies or humanized 20 antibodies. Such non-naturally occurring antibodies can be constructed using solid phase peptide synthesis, can be produced recombinantly or can be obtained, for example, by screening combinatorial libraries consisting of variable heavy chains and variable light chains as described by Huse et al., *Science* **246**:1275-1281 (1989), which is incorporated 25 herein by reference.

One skilled in the art would know that purified BAG family protein, which can be prepared from natural sources or synthesized chemically or produced 30 recombinantly, or portions of a BAG family protein, including a portion of human BAG family protein such as a synthetic peptide as described above, can be used as an immunogen. Such peptides useful for raising an antibody include, for example, peptide portions of the N-terminal 85 35 amino acids or the BAG domain of any of the human BAG

proteins (see Figure 1B). A particularly advantageous use of such a protein is for the immunostaining, wherein the methods provides a process to contrast the immunostaining of BAG-family proteins in carcinoma cells with adjacent
5 non-neoplastic prostatic epithelial and basal cells which are generally present in the same tissue sections. These results would be correlated with a Gleason grade to determine whether any of the BAG-family proteins tend to be expressed at higher or lower levels in histologically
10 advanced tumors. From this process a determination can be made as to degree at which the disease is progressing in a given patient, i.e., a prognosis can be made.

Non-immunogenic fragments or synthetic peptides of BAG proteins can be made immunogenic by coupling the
15 hapten to a carrier molecule such bovine serum albumin (BSA) or keyhole limpet hemocyanin (KLH), as described in Example IV, below. In addition, various other carrier molecules and methods for coupling a hapten to a carrier molecule are well known in the art and described, for
20 example, by Harlow and Lane, *Antibodies: A laboratory manual* (Cold Spring Harbor Laboratory Press, 1988), which is incorporated herein by reference.

EXAMPLES

The following examples are given to enable those
25 skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

EXAMPLE IIsolation and Characterization
of BAG-family cDNA Sequences

This example describes methods for isolating and
5 characterizing of BAG-family cDNA sequences from human,
nematode and yeast.

A. Cloning of human BAG cDNA sequences

Yeast two-hybrid library screening of a human
Jurkat cell cDNA library was performed as described by
10 Takayama et al., EMBO J., 16:4887-96 (1997); Matsuzawa et
al., EMBO J., 17:2736-2747 (1998), which are incorporated
herein by reference) using EGY48 strain yeast transformed
with pGilda-Hsc70/ATPase (67-377 amino acids) and the lacZ
reporter plasmid pSH18-34. Of the resulting $\sim 5 \times 10^6$
15 transformants, 112 Leu⁺ colonies were obtained after
1 week incubation at 30°C. Assay of β -galactosidase (β -gal)
activity of these colonies resulted in 96 clones. Mating
tests were then performed using RFY206 yeast strain
transformed with pGilda, pGilda mBAG-1 (1-219), or pGilda
20 Hsc70/ATPase. Of these, 66 displayed specific interactions
with Hsc70/ATPase. The pJG4-5 cDNAs were recovered using
KC8 *E. coli* strain which is auxotrophic for tryptophan
(Trp). DNA sequencing revealed 3 partially overlapping
human BAG-1, 4 identical and one overlapping cDNAs encoding
25 BAG-2, and 2 partially overlapping BAG-3 clones.

Using the above described yeast two-hybrid screen
with the ATPase domain of Hsc70 as "bait", several human
cDNAs were cloned which encode portions of BAG-1 or of two
other BAG-1-like proteins which are termed BAG-2 (SEQ ID
30 NO:4) and BAG-3 (SEQ ID NO:6). The longest of the cDNAs
for BAG-2 (SEQ ID NO:3) and BAG-3 (SEQ ID NO:5) contained
open reading frames (ORFs) of 207 and 162 amino acids,
respectively, followed by stop codons. All BAG-1 (SEQ ID

NO:1), BAG-2 (SEQ ID NO:3) and BAG-3 (SEQ ID NO:5) cDNAs obtained by two-hybrid library screening with Hsc70/ATPase contained a conserved domain of about 40-50 amino acids which are termed the "BAG" domain and are shown in Figure 5 10. These results demonstrate that a family of BAG-1-related proteins all contain a conserved ~45 amino acid region near their C-terminus that binds Hsc70/Hsp70.

B. Identification of additional BAG-family proteins

A search of the translated Genbank database using 10 the bBLAST and FASTA search programs also identified human ESTs that provided sequences for further investigation of BAG-family proteins. The putative BAG-4 (SEQ ID NO:8) and BAG-5 (SEQ ID NO:10) proteins contain BAG-domains that share the greatest sequence similarity with the BAG-domain 15 of BAG-3 (SEQ ID NO:6). These were designated BAG-4 (Accession number AA693697, N74588) and BAG-5 (Accession number AA456862, N34101). BAG-4 has 62% identity and ~81% similarity to BAG-3, and BAG-5 has 51% identity and ~75% similarity to BAG-3.

20 Additional BAG-family orthologues or homologues were also identified using computer-based searches and resulted in BAG-family homologue in the nematode *C. elegans* and the fission yeast *S. pombe*. The *C. elegans* genome encodes two apparent BAG-family proteins, which are most 25 similar in their overall sequences to the human BAG-1 (Afo39713, gi:2773211) (SEQ ID NO:12) and BAG-2 (SEQ ID NO:14) (Afo68719, gi:3168927). The *S. pombe* contains two BAG-family proteins that share the greatest overall sequence similarity with human BAG-1 (Alo23S54, gi/3133105 30 and Alo23634, gi/3150250). The human and *C. elegans* BAG-1 proteins as well as *S. pombe* BAG-1A all have ubiquitin-like domains near their N-termini (see Figure 10A) of unknown function.

The overall predicted amino acid sequences of the *C. elegans* BAG-1 (SEQ ID NO:12) and *S. pombe* BAG-1A (SEQ ID NO:16) proteins are ~18% identical (~61% similar) and ~17% identical (~64% similar), respectively, to human BAG-1, implying origin from a common ancestral gene. The *C. elegans* BAG-1 protein (SEQ ID NO:12), however, contains a 5 to 7 amino acid insert in its BAG-domain as compared to the human, murine, and yeast BAG-1 homologues (see Figure 10B), and is more similar to BAG-2 (SEQ ID NO:4) in regard to its BAG-domain. *C. elegans* and human BAG-2 also may be derived from a common ancestor as the C-terminal 225 amino acid region which encompasses both the BAG domain and upstream region of both *C. elegans* and human BAG-2 share ~34% amino acid sequence identity and ~70% similarity. The human BAG-2 protein (SEQ ID NO:4), however, contains a 9 amino acid insert in its BAG-domain compared to its *C. elegans* counterpart (see Figure 10B). Evolutionary-tree prediction algorithms suggest that human and *C. elegans* BAG-2 represent a distinct branch of the BAG-family that is more evolutionarily distant from the other BAG-family proteins. None of the predicted BAG-family proteins contain recognizable regions analogous to those found in other Hsc70 regulatory proteins, such as the J-domains and G/F-domains of DnaJ family proteins and the Tetratricopeptide Repeat (TR) domains of Hip/Hop family proteins.

C. Yeast two-hybrid assay of BAG binding to Hsc70/ATPase

The longest of the cDNAs obtained for the BAG-2 and BAG-3 proteins were expressed with N-terminal transactivation (TA) domains in yeast and tested by yeast two-hybrid assay for interactions with fusion proteins consisting of Hsp70/ATPase or a variety of unrelated proteins (Fas, Siah, Fadd) containing N-terminal LexA DNA-binding domains. TA-BAG-2 and TA-BAG-3 demonstrated

positive interactions with LexA-Hsc70/ATPase, resulting in transactivation of a *lacZ* reporter gene that was under the control of LexA operators (Figure 11A). No interactions with LexA-Fas (cytosolic domain), LexA-Siah, LexA-Fadd, or LexA were detected (see Figure 11A) demonstrating that the BAG-2 and BAG-3 proteins interact specifically with Hsc70/ATPase. Specific two-hybrid interactions between Hsc70/ATPase and either BAG-2 or BAG-3 were also observed when BAG-2 and BAG-3 were expressed as LexA DNA-binding domain fusion proteins and Hsc70/ATPase was fused with a TA domain (see Figure 11A; right panel). These results demonstrate that similarly to BAG-1, BAG-2 and BAG-3 specifically interact with Hsc70/ATPase.

In order to determine whether the BAG proteins are capable of forming heterodimers, coexpression of BAG-2 and BAG-3 in the yeast two-hybrid assay was also performed. Coexpression of BAG-2 and BAG-3 failed to show interaction with BAG-1 or a deletion mutant of BAG-1 (ΔC) which is missing part of its C-terminal domain required for Hsp70/Hsc70 binding suggest that these proteins do not form heterodimers.

D. Isolation and characterization of the complete open reading frame sequences of BAG-2 and BAG-3

In order to deduce the complete ORFs of BAG-2 and BAG-3, a λ -phage cDNA library was screened as follows, using hybridization probes derived from the two-hybrid screening. A human jurkat T-cell λ -ZapII library cDNA library (Stratagene) was screened by hybridization using ^{32}P -labeled purified insert DNA from the longest of the human BAG-2 (clone #11) and human BAG-3 (clone #28) cDNA clones. From about one million clones screened, 38 BAG-2 and 23 BAG-3 clones were identified, cloned, and their cDNA inserts recovered as pSKII plasmids using a helper phage method (Stratagene). DNA sequencing of λ -phage derived

human BAG-2 cDNA clones revealed an ORF encoding a predicted 211 amino acid protein, preceded by an in-frame stop codon. The longest human BAG-3 λ -phage cDNA clone contains a continuous ORF of 682 amino acids followed by a
5 stop codon, but without an identifiable start codon (see Figure 10A).

Although BAG-1L (SEQ ID NO:2), BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), and BAG-3 (SEQ ID NO:6) all contain a homologous BAG domain
10 near their C-terminus, the N-terminal regions of these proteins are dissimilar. Using a combination of search tools (Prosite Search: PP search, using the Prosite pattern database, BCM Search Launcher, Baylor College of Medicine, and Blocks Search), it was determined that the BAG-2 N-
15 terminal region contains potential kinase phosphorylation sites but otherwise shares no apparent similarity with other proteins or known functional domains.

In contrast, the predicted N-terminal region BAG-3 contains a WW domain as shown in Figure 10A. WW
20 domains have been identified in a wide variety of signaling proteins, including a Yes kinase adaptor protein (YAP), the Na⁺-channel regulator Nedd4, formin-binding proteins, dystrophin, and the peptidyl prolyl cis-trans-isomerase Pin-1. These roughly 40 amino acid domains mediate protein
25 interactions and bind the preferred peptide ligand sequence xPPxY (Sudol., TIBS, 21: 161-163, 1996, which is incorporated herein by reference).

EXAMPLE IIIn vitro Association of
BAG proteins and Hsc70/ATPase

This example demonstrates that BAG-2 (SEQ ID
5 NO:4) and BAG-3 (SEQ ID NO:6) bind Hsc70/ATPase in various
in vitro assays.

A. Solution binding assay of BAG-2 and BAG-3 to
Hsc70/ATPase

Association of BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ
10 ID NO:6) with Hsc70/ATPase was determined by an *in vitro*
protein binding assay where Hsc70/ATPase or BAG-family
proteins were expressed in bacteria as Glutathione S-
Transferase (GST) fusion proteins. Purified cDNA sequences
encoding residues 5 to 211 of human BAG-2 (clone #11) and
15 the C-terminal 135 amino acids of human BAG-3 (clone #28)
(see Figure 10A) were subcloned into the EcoRI/Xho I sites
of pGEX4T-1 prokaryotic expression plasmid (Pharmacia;
Piscataway, NJ). These plasmids as well as pGEX4T-1-BAG-1,
pGEX-4T-1-BAG-1 (Δ C), and pGEX-4T-1-XL which have been
20 described previously (Takayama et al., *supra* (1997); Xie et
al., Biochemistry, 37:6410-6418, (1998), which are
incorporated herein by reference), were expressed in XL-1
blue strain *E. Coli* (Stratagene, Inc., La Jolla, CA).
Briefly, a single colony was inoculated into 1L of LB media
25 containing 50 μ g/ml ampicillin and grown at 37°C overnight.
The culture was then diluted by half with fresh
LB/ampicillin and cooled to room temperature for 1 hr,
before inducing with 0.4mM IPTG for 6 h at 25°C.

Cells were recovered and incubated with 0.5 mg/ml
30 lysozyme in 50 mM Tris (pH 8.0), 150 mM NaCl, 1% Tween-20,
0.1% 2-mercaptoethanol, 5 mM EDTA, 1 mM PMSF and a mixture

of other protease inhibitors obtained from Boehringer Mannheim (1697498) at room temperature for 0.5 h, followed by sonication. Cellular debris were pelleted by centrifugation at 27,500g for 10 min and the resulting supernatants were incubated with 30 ml of glutathione-Sepharose (Pharmacia) at 4°C overnight. The resin was then washed with 20 mM Tris (pH 8.0), 150 mM NaCl, 0.1% Tween-20, and 0.1% 2-mercaptoethanol until the OD 280nm reached <0.01. For removal of GST, the resin with immobilized GST-fusion protein was incubated with 10U of thrombin (Boehringer, Inc.) at 4°C in 20 mM Tris (pH 8.0), 150 mM NaCl, 0.1% Tween-20, 0.1% 2-Mercaptoethanol, and 2.5 mM CaCl₂ overnight. Released proteins were then purified on Mono Q (HR10/10, Pharmacia) by FPLC using a linear gradient of 0.5M NaCl at pH 8.0 and dialyzed into chaperone assay buffer.

The ability of BAG-2 (SEQ ID NO:4) or BAG-3 (SEQ ID NO:6) to bind Hsc70/ATPase in solution was then examined. GST control or GST-BAG proteins were immobilized on glutathione-Sepharose and tested for binding to ³⁵S-labeled *in vitro* translated (IVT) proteins. Immunoprecipitation and *in vitro* GST-protein binding assays were performed as described by Takayama et al., *supra* (1997), using pCI-Neo flag or pCDNA3-HA into which human Bag-2 (clone #11) or human BAG-3 (clone #28) had been subcloned for *in vitro* translation of ³⁵S-L-methionine labeled proteins or expression in 293T cells. As shown in Figure 11B, ³⁵S-Hsc70/ATPase bound *in vitro* to GST-BAG-1, GST-BAG-2, and GST-BAG-3 but not to GST-BAG-1(ΔC) or several other control proteins. BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), and BAG-3 (SEQ ID NO:6) also exhibited little or no binding to themselves or to each other, demonstrating that these proteins do not strongly homo- or hetero-dimerize or oligomerize. It should be noted, however, that BAG-2 (SEQ

ID NO:4) displayed weak interactions with itself in binding assays and produced a positive result in yeast two-hybrid experiments, demonstrating that it can have the ability to self-associate.

5 B. Binding of BAG proteins to Hsc70 in vivo

The ability of BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) proteins to interact in cells with Hsc70 was tested by expressing these proteins with N-terminal Flag epitope tags in 293T human epithelial cells using co-immunoprecipitation assays as described previously (Takayama et al., *supra* (1997)). cDNAs encoding the λ -phage cloned regions of BAG-2 and BAG-3 were subcloned in-frame into pcDNA3-Flag. Anti-Flag immune complexes prepared from 293T cells after transfection with plasmids encoding Flag-BAG-1, Flag-BAG-2, or Flag-BAG-3 were analyzed by SDS-PAGE/immunoblot assay. As shown in Figure 10C, antiserum specific to Hsc70 detected the presence of BAG proteins associated with Hsc70, whereas control immune-complexes prepared with IgG1 as well as anti-Flag immune complexes prepared from cells transfected with Flag-tagged control proteins, Daxx and Apaf-1, did not contain Hsc70 associated protein. These results further demonstrate that BAG-family proteins specifically bind to Hsc70.

25 C. BIAcore assay of BAG protein binding to the ATPase domain of Hsc70

BAG-1 (beginning at residue 116 of SEQ ID NO:2) is known to bind tightly to the ATPase domain of Hsc70 (Stuart et al., *J. Biol. Chem.*, In Press (1998)). BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) proteins were therefore, examined for their ability to bind to Hsc70/ATPase. The affinity and binding kinetics of BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) to Hsc70/ATPase was also compared to that of BAG-1 (beginning at residue 116 of

SEQ ID NO:2) for Hsc70/ATPase, using a surface plasmon resonance technique (BIAcore) which has been described previously (Stuart et al., *supra*, (1998) which is incorporated herein by reference).

5 BAG-family proteins were produced in bacteria and purified to near homogeneity as shown in Figure 12A and described above in Example I. The purified BAG-1 (beginning at residue 116 of SEQ ID NO:2), -2 (SEQ ID NO:4), and -3 (SEQ ID NO:6) proteins were then immobilized
10 on biosensor chips and tested for their interactions with Hsc70 in the soluble phase. Kinetic measurements were performed using a BIAcore-II instrument with CM5 sensor chip and Amine Coupling Kit (Pharmacia Biosensor AB, Sweden). Briefly, for immobilization of proteins, the
15 sensor chip was equilibrated with HK buffer (10 mM Hepes (pH 7.4), 150 mM KCL) at 5 μ l/min, then activated by injecting 17 μ l of 0.2M N-ethyl-N'-(3-diethylaminopropyl)-carbodiimide and 0.05M N-hydroxysuccinimide (NHS/EDC) followed by 35 μ l of the protein of interest, in 10 mM
20 acetate, pH 3.5-4.5. Excess NHS-ester on the surface was deactivated with 17 μ l 1M ethanolamine-HCL (pH8.5). After immobilization, 5 μ l of regeneration buffer (50 mM phosphate (pH 6.8) and 4M GuHCl) was injected. For binding assays, Hsp70 (Sigma, H8778) was dissolved in HK buffer, and
25 injected at 10 μ l/min across the prepared surface at various concentrations. The surface was regenerated after each injection with 5 μ l of regeneration buffer. The rate constants k_{ass} and k_{diss} were generated with BIAevaluation software 3.01 (Pharmacia Biosensor AB). Addition of Hsc70
30 to chips containing BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4) or BAG-3 (SEQ ID NO:6) resulted in concentration-dependent binding, as reflected by an increase in the Response Units (RU) measured at the chip surface (shown in Figure 3B). In contrast, Hsc70
35 failed to display interactions in BIAcore assays with a variety of control proteins as well as a mutant of BAG-1

lacking a C-terminal portion of the BAG domain which is required for Hsc70-binding (Figure 3B). Furthermore, flowing of various control proteins such as GST, BSA and Bcl-XL over the BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), or BAG-3 (SEQ ID NO:6) chips resulted in negligible interaction. These results further demonstrate the specificity with which BAG-family proteins interact with and bind to Hsc70.

The rates of Hsc70 binding to BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), and BAG-3 (SEQ ID NO:6) proteins were similar, following pseudo first-order kinetics with estimated association rate constants (k_a) of 2.1 , 2.1 and $2.4 \times 10^5 \text{ M}^{-1} \text{ sec}^{-1}$, respectively. After allowing binding of Hsc70 to immobilized BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), or BAG-3 (SEQ ID NO:6) to reach plateau levels, the chaperone was removed from the flow solution and the dissociation rate was monitored. BAG-1 (beginning at residue 116 at SEQ ID NO:2) and BAG-2 (SEQ ID NO:4) exhibited similar dissociation rates, with relatively slow loss of Hsc70 from the chip surface, resulting in estimated dissociation rate constants (k_d) of 3.0 and $5.0 \times 10^{-4} \text{ sec}^{-1}$, respectively (see Figure 3B). In contrast, Hsc70 dissociated more rapidly from biosensor chips containing BAG-3 (see Figure 3B), yielding an estimated k_d of $1.7 \times 10^{-3} \text{ sec}^{-1}$. From the kinetic data, the apparent affinities ($K_D = k_d/k_a$) were calculated for binding of Hsc70 to BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), and BAG-3 (SEQ ID NO:6) and were estimated to equal about $K_D = 1.4 \text{ nM}$, $K_D = 2.4 \text{ nM}$, and $K_D = 7.4 \text{ nM}$, respectively. These results demonstrate that the interactions of BAG-family proteins with Hsc70 occur with apparent affinities sufficient for physiological relevance.

EXAMPLE III

BAG-family proteins inhibit
Hsp70/Hsc70-dependent protein folding

This example demonstrates that BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) proteins inhibit Hsp70/Hsc70-dependent refolding of denatured proteins similarly to a BAG-1 (beginning at residue 116 of SEQ ID NO:2) protein.

The effects of BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) protein on Hsp70/Hsc70-dependent protein refolding was determined using *in vitro* protein refolding assays similar to those described previously by Takayama et al., *supra*, 1998; Terada et al., *J Cell Biol.*, 139:1089-1095, 1997, which are incorporated herein by reference. Briefly, luciferase (20 μ M) was denatured in 25 mM Hepes-KOH, pH 7.2, 50 mM potassium acetate, 5 mM DTT, 6M guanidine hydrochloride at ~25°C for 1 h. Denatured luciferase was diluted 1:40 into 25 mM Hepes-KOH, pH 7.2, 50 mM potassium acetate, 5 mM DTT. Hsc70 (1.8 μ M), DnaJ (StressGen, Inc.) (0.9 μ M), and various purified recombinant proteins as indicated were added to refolding buffer (30 mM Hepes-KOH, pH 7.6, 120 mM potassium acetate, 3mM magnesium acetate, 2 mM DTT, 2.5 mM ATP) with 0.2 volume of diluted denatured luciferase to a final concentration of 0.1 μ M. Luciferase activity was measured after 1.5 hr incubation at 35°C.

The combination of Hsc70 and DnaJ resulted in ATP-dependent refolding of chemically denatured firefly luciferase, with function of over half the denatured enzyme restored in a 90 minute reaction, as monitored by a chemiluminescence assay. In contrast, neither Hsc70 nor DnaJ alone were able to induce substantial refolding of denatured luciferase. Furthermore, little spontaneous

restoration of luciferase activity was observed with control proteins, BSA, GST or Bcl-XL (see Figure 4A).

Addition of recombinant purified BAG-1 (beginning
5 at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), or
BAG-3 (SEQ ID NO:6) to the above assays in amounts
equimolar to Hsc70 (1.8 μ M) resulted in striking inhibition
of luciferase refolding. BAG-2 (SEQ ID NO:4) and BAG-3
(SEQ ID NO:6) displayed somewhat greater inhibitory
10 activity than BAG-1 (beginning at residue 116 of SEQ ID
NO:2) as shown in Figure 4A. In contrast, the BAG-1 (Δ)
protein, which fails to bind Hsc70 as well as several other
control proteins, had no effect on luciferase refolding.

In an additional refolding assay, described
15 previously by Minami et al., J Biol. Chem. 271:19617-24,
1996), purified Hsc70 and human DnaJ homolog Hdj-1 (Hsp 40)
were used with additional cofactors provided in
reticulocyte lysates (5% v:v) to produce a system capable
of refolding denatured luciferase. Briefly, additional
20 cofactors included, recombinant Luciferase (Promega:
QuantiLum TM), that had been heat denatured at 42°C for 10
min, 1.8 μ M Hsc70 (Sigma; purified from bovine brain), 0.9
 μ M Hsp40, and various recombinant purified proteins.
Luciferase activity was measured (Promega luciferase assay
25 kit) using a luminometer (EG&G Berthold, MicroLumat
luminometer, Model #LB96P). All results were normalized
relative to non-denatured luciferase that had been
subjected to the same conditions. Control reactions
lacking ATP, Hsc70, or Hsp40 resulted in negligible
30 luciferase refolding.

Various amounts of purified BAG-1 (beginning at
residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), or BAG-3
(SEQ ID NO:6), relative to amounts of Hsc70 were used in
the above-described protein refolding assay. Addition of
35 BAG-family proteins resulted in a concentration-dependent

inhibition of Hsc70 chaperone activity. Furthermore, the BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) inhibition of Hsc70 chaperone activity was demonstrated to be as potent as that observed for BAG-1 (beginning at residue 116 of SEQ ID NO:2). In contrast, the BAG-1 (Δ C) mutant as well as other control proteins did not suppress Hsc70-mediated refolding of denatured luciferase. These results indicate that BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) can inhibit Hsc70/Hsp70 dependent protein refolding activity to the same extent as BAG-1 (beginning at residue 116 of SEQ ID NO:2).

B. BAG competes with Hip for binding to Hsc70.

It is known that BAG-1 competes with Hip for binding to Hsc70, with these proteins exerting opposite effects on Hsc70-mediated protein refolding (Hohfeld, J., and Jentsch, S., *Embo J.*, 16:6209-6216, 1997, which is incorporated herein by reference). In order to determine whether BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6) also compete with Hip for binding to Hsc70, refolding assays were performed as described above in the presence of Hip protein.

Hip was purified as His₆-protein. The fusion protein was induced from pET28-Hip (V. Prapapanich et al., *Mol Cell Biol.*, 18:944-952, 1998, which is incorporated herein by reference) with 0.1 mM IPTG at 25°C for 6h in BL21 cells. Cells from 1L of culture were resuspended into 50 ml of 50 mM Phosphate buffer (pH 6.8), 150 mM NaCl, and 1% (v/v) Tween-20 and then incubated with 0.5 mg/ml lysozyme at 25°C for 0.5h, followed by sonication. After centrifugation at 27,500g for 10 min, the resulting supernatant was mixed with 15 ml nickel resin (Qiagen, Inc.) at 4°C for 3 h with 25 mM imidazol. The resin was then washed with 50 mM phosphate buffer (pH 6.8), 25 mM imidazol, 150 mM NaCl and 0.1% Tween-20 until the OD_{280nm}

reached a value of <0.01. His₆-Hip protein was eluted with 250 mM imidazol in washing buffer (Qiagene, Inc.) and purified on Mono Q (HR10/10 Pharmacia) by FPLC using a linear gradient of 0.5M NaCl at pH 8.0, followed by
5 dialysis in chaperone assay buffer.

In the refolding assay reactions, addition of purified Hip at equimolar concentrations relative to BAG-1 (beginning at residue 116 of SEQ ID NO:2), BAG-2 (SEQ ID NO:4), or BAG-3 (SEQ ID NO:6) (1.8 μM) completely negated
10 the inhibitory effects of the BAG-family proteins on refolding of denatured luciferase (see Figure 4C). These results demonstrate that the suppression of Hsc70 chaperone activity by BAG-family proteins is reversible, and that Hip antagonizes the effects of not only BAG-1 (beginning at
15 residue 116 of SEQ ID NO:2), but also of BAG-2 (SEQ ID NO:4) and BAG-3 (SEQ ID NO:6).

In summary, these results demonstrate that BAG-family proteins all contain a conserved BAG domain near their C-terminus that binds Hsc70/Hsp70, and that human
20 BAG-family proteins can bind with high affinity to the ATPase domain of Hsc70 and inhibit its chaperone activity through a Hip-repressable mechanism.

EXAMPLE IV

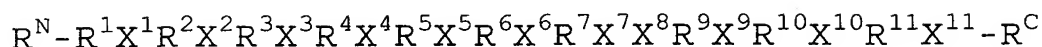
EXPANDED NUCLEIC ACID AND AMINO ACID SEQUENCES FOR HUMAN BAG-3, BAG-4 AND BAG-5

25

Following the procedures disclosed herein, the nucleic acid and amino acids sequences to human BAG-3, BAG-4 and BAG-5 were further expanded. The expanded sequences for BAG-3, BAG-4 and BAG-5 are shown in
30 Figures 15, 16 and 17, respectively, with their respective sequence identification numbers, "SEQ ID NO"s.

We claim:

1. A compound of the formula,



wherein,

- 5 R^N is a group of about 1 to 552 independently selected amino acids;
- R^1 is a group of 3 independently selected amino acids;
- 10 X^1 is an amino acid with a charged or uncharged R group;
- R^2 is a group of 7 independently selected amino acids;
- X^2 is an amino acid with a charged R group;
- 15 R^3 is a group of 5 independently selected amino acids;
- X^3 is an amino acid with an apolar R group;
- R^4 is a group of 3 independently selected amino acids;
- X^4 is an amino acid with charged R group;
- 20 R^5 is a single independently selected amino acid;
- X^5 is an amino acid with apolar or uncharged R group;
- R^6 is a group of 15 independently selected amino acids;
- 25 X^6 is an amino acid with a charged or uncharged R group;
- R^7 is a group of 2 independently selected amino acids;
- X^7 is an amino acid with a charged R group;
- 30 X^8 is an amino acid with a charged R group;
- R^9 is a group of 2 independently selected amino acids;
- X^9 is an amino acid with an apolar R group;

R¹⁰ is a group of 3 independently selected amino acids;
X¹⁰ is an amino acid with an uncharged R group;
R¹¹ is a group of 2 independently selected amino acids;
5 X¹¹ is an amino acid with an apolar R group; and
R^C is a group of about 1 to 100 independently selected amino acids.

2. A substantially purified nucleic acid
10 molecule having a nucleotide sequence corresponding to or complementary to at least 20 nucleotides from a nucleotide sequence selected from the group consisting of (SEQ ID NO:1), (SEQ ID NO:3), (SEQ ID NO:5), (SEQ ID NO:7), (SEQ ID NO:9), (SEQ ID NO:19), (SEQ ID NO:21) and (SEQ ID NO:23).

15 3. The nucleic acid of claim 2 having a nucleotide sequence corresponding to or complementary to a nucleotide sequence that encodes a functionally active BAG family protein selected from the group consisting of (SEQ ID NO:2), (SEQ ID NO:4), (SEQ ID NO:6), (SEQ ID NO:8), (SEQ ID NO:10), (SEQ ID NO:20), (SEQ ID NO:22) and (SEQ ID NO:24).

25 4. The nucleic acid of claim 3 selected from the group consisting of (SEQ ID NO:1), (SEQ ID NO:3), (SEQ ID NO:5), (SEQ ID NO:7), (SEQ ID NO:9), (SEQ ID NO:19), (SEQ ID NO:21) and (SEQ ID NO:23).

5. The nucleic acid of claim 3 complementary to a nucleotide sequence that encodes a functionally active BAG protein selected from the group consisting of (SEQ ID NO:2), (SEQ ID NO:4), (SEQ ID NO:6), (SEQ ID NO:8), (SEQ ID NO:10), (SEQ ID NO:20), (SEQ ID NO:22) and (SEQ ID NO:24).

6. A substantially purified nucleic acid molecule having the nucleotide sequence of (SEQ ID NO:3).

7. A substantially purified nucleic acid molecule having the nucleotide sequence of (SEQ ID NO:5).

8. A substantially purified nucleic acid molecule having the nucleotide sequence of (SEQ ID NO:7).

5

9. A substantially purified nucleic acid molecule having the nucleotide sequence of (SEQ ID NO:9).

10. A substantially purified nucleic acid molecule having the nucleotide sequence of (SEQ ID NO:19).

10

11. A substantially purified nucleic acid molecule having the nucleotide sequence of (SEQ ID NO:21).

12. A substantially purified nucleic acid molecule having the nucleotide sequence of (SEQ ID NO:23).

13. A substantially purified BAG family protein encoded by the nucleic acid molecule of claim 1.

14. A substantially purified BAG family protein comprising of the amino acid sequence selected from the group consisting of (SEQ ID NO:2), (SEQ ID NO:4), (SEQ ID NO:6), (SEQ ID NO:8), (SEQ ID NO:10), (SEQ ID NO:20), (SEQ ID NO:22) and (SEQ ID NO:24) or a fragment, a derivative or a mimetic thereof.

20

15. A substantially purified protein corresponding to the amino acid sequence of 157 to 204 of (SEQ ID NO:2).

25

16. A substantially purified protein corresponding to the amino acid sequence of 272 to 319 of (SEQ ID NO:2).

17. A substantially purified protein corresponding to the amino acid sequence of 164 to 211 of (SEQ ID NO:4).

18. A substantially purified protein
5 corresponding to the amino acid sequence of 418 to 510 of (SEQ ID NO:20).

19. A substantially purified protein corresponding to the amino acid sequence of 378 to 457 of (SEQ ID NO:22).

20. A substantially purified protein
10 corresponding to the amino acid sequence of 6 to 97 of (SEQ ID NO:24).

21. A substantially purified protein
15 corresponding to the amino acid sequence of 180 to 257 of (SEQ ID NO:24).

22. A substantially purified protein corresponding to the amino acid sequence of 272 to 349 of (SEQ ID NO:24).

23. A substantially purified protein
20 corresponding to the amino acid sequence of 362 to 444 of (SEQ ID NO:24).

24. A pharmaceutical composition comprising a nucleic acid molecule of claim 1 useful for modulating tumor cell proliferation, cell migration and metastasis,
25 and steroid hormone receptor function.

25. A method of modulating tumor cell proliferation, cell migration and metastasis, and steroid hormone receptor function by administering a nucleic acid molecule of claim 1.

26. A pharmaceutical composition comprising a substantially purified BAG family protein comprising of the amino acid sequence selected from the group consisting of (SEQ ID NO:2), (SEQ ID NO:4), (SEQ ID NO:6), (SEQ ID NO:8),
5 (SEQ ID NO:10), (SEQ ID NO:20), (SEQ ID NO:22) and (SEQ ID NO:24), or a fragment, a derivative or a mimetic thereof, useful for modulating tumor cell proliferation, cell migration and metastasis, and steroid hormone receptor function.

10 27. A method of modulating tumor cell proliferation by administering a pharmaceutical composition of claim 26.

28. A method of modulating cell migration and metastasis by administering a pharmaceutical composition of
15 claim 26.

29. A method of modulating steroid hormone receptor function by administering a pharmaceutical composition of claim 26.

30. A substantially purified antibody that
20 specifically binds to a BAG family protein of claim 14.

31. The antibody of claim 30, wherein said antibody is a monoclonal antibody.

32. A method for detecting the presence of a BAG family protein in a sample, comprising the steps of:

- a. obtaining the sample;
- b. adding to said an antibody of claim 11 under suitable conditions for the binding of said antibody with the BAG family protein; and
- c. detecting said bound BAG family protein.

33. A method for detecting the presence of a first nucleic acid molecule that encodes a BAG family protein in a sample, comprising the steps of:

- a. obtaining the sample;
- b. adding to said sample a second nucleic acid molecule capable of hybridizing with said first nucleic acid molecule under suitable conditions for the binding of said second nucleic acid molecule with said first nucleic acid molecule; and
- c. detecting said hybridized first and second nucleic acid molecules.

34. A method of determining the risk of metastatic spread of cancer or prognosis of cancer patients by determining the level of expression of a BAG-family protein.

FIGURE 1

90 AGCCGCGCT CAGCTTCAT GCGCTGCGG TCACACATG CCGCTCTGC L A Q R G G A R R P R G D R E
 BAG-1L
 180 CCGCTGGTT CCGCGCTCG CCGCTTCCG CCGCGCGCG GAGCGCGG GCGCTGCGG GCGCTGCGG TCGCTGCGG
 R L G S R L R A L R A L R P G R E P R Q S E P P A Q R G P P P S R
 270 CCGTCACTG CCGCGCTCG CCGCGCGCG CCGCGCGCG CCGCGCTCG GCGCTGCGG GCGCTGCGG GCGCTGCGG
 R P P A R S T A S G H D R P T R G A A A G A R R P R M K K K
 BAG-1M
 360 ACCCGCGCG CCGTCACTG CCGCGCGCG CCGCGCGCG CCGCTGCGG GCGCGCGG CCGCTGCGG GCGCGCGG
 T R R R S T R S E E L T R S E E L T L S E A T W S E E A T
 450 CAGCTGCGG AGCGCGCGG CCGCGCGCG CCGCGCGCG CCGCGCTCG GCGCGCGG CCGCGCGG GCGCGCGG
 Q S E E A T Q G E E M N R S Q E V T R D E E S T R S E E V T
 BAG-1
 540 AGCGCGCGG TCGCGCGCG CCGCGCGCG CCGCGCGCG CCGCTGCGG GCGCGCGG CCGCTGCGG GCGCGCGG
 R E E M A A A G L T V T V T H S N E K H D L H V T S Q Q G S
 630 AGTCACTG TCGCGCGG CCGCGCGCG CCGCGCGCG CCGCTGCGG GCGCGCGG CCGCTGCGG GCGCGCGG
 S E P V V Q D L A Q L A Q V V E E V I G V P Q S F Q K L I F K G K
 720 TCGTCACTG AACTCACTG CCGCGCGCG CCGCGCGCG CCGCTGCGG GCGCGCGG CCGCTGCGG GCGCGCGG
 S L K E M E T P L S A L G I Q D G C R V M L I G K K N S P Q
 810 CAGCTGCGG AACTCACTG CCGCGCGCG CCGCGCGCG CCGCTGCGG GCGCGCGG CCGCTGCGG GCGCGCGG
 E E V E L K K L K H L E K S V E K I A D Q L E E L N K E L T
 900 GCGTCACTG AGCGCGCGG CCGCGCGCG CCGCGCGCG CCGCTGCGG GCGCGCGG CCGCTGCGG GCGCGCGG
 G I Q Q G F L P K D L Q A E A L C K L D R R V K A T I E Q F
 990 ACGTCACTG TCGCGCGG CCGCGCGCG CCGCGCGCG CCGCTGCGG GCGCGCGG CCGCTGCGG GCGCGCGG
 M K I L E E I D T L I L P E N F K D S R L K R K G L V K K V
 1080 CCGCTGCGG TCGCGCGG CCGCGCGCG CCGCGCGCG CCGCTGCGG GCGCGCGG CCGCTGCGG GCGCGCGG
 Q A F L A E C D T V E Q N I C Q E T E R L Q S T N F A L A E
 1170 TCGCTGCGG CAGCGCGG CCGCTGCGG CCGCTGCGG CCGCTGCGG GCGCGCGG CCGCTGCGG GCGCGCGG
 TCGCTGCGG CCGCTGCGG CCGCTGCGG CCGCTGCGG CCGCTGCGG GCGCGCGG CCGCTGCGG GCGCGCGG
 1260 GCGCTGCGG CCGCTGCGG CCGCTGCGG CCGCTGCGG CCGCTGCGG GCGCGCGG CCGCTGCGG GCGCGCGG
 TCGCTGCGG CCGCTGCGG CCGCTGCGG CCGCTGCGG CCGCTGCGG GCGCGCGG CCGCTGCGG GCGCGCGG
 1291 TCGCTGCGG CCGCTGCGG CCGCTGCGG CCGCTGCGG CCGCTGCGG GCGCGCGG CCGCTGCGG GCGCGCGG

FIGURE 2A

90 GCAGCCGCGG TGTCGCGAAG TCCTCCCGGG TTGCCCCCGC GCGTCAAG GAGGGCGGG CGCCGCGTTG GTACGCGCGA CCCTGCAGCC
 180 CAGGAGCGC TCCACTCGCT GCGCGCGAG GCGCGGTGAC CTCTTGCTA CCCCCTCGT GAGGCTTAGA TGGCTCAGGC GAAATCAAC
 270 GCTAAGCCA ACCAGGGGCG CTTCTGCGC TCCTCCTCCA TGGCTGACG CTCCAGCCGC CTGCTGAGG GCCTGGACCA GCTGAGGCTC
 360 AGGTTGAGG CTTTGAGAGA AGCAGCAACT GCTGTTGAGC AAGAGAGAGA AATCCTTCTG GAATGATCC ACGTATCCA AATATGCCAG
 450 GACATGAGC AGATCAGTGA CGGAGAGAGA GAGCAATTAA ATCTGACTGC AACCCTTGG ATGGGAGAA CTCTCACCCT TGAAGTGTCA
 540 GTAGARACAA TTAGAAACCC CCAGCAGCAA GAATCCCTAA AGCATGCCAC AGGATTATT GATGAGGTGG TCAATAGTT TCTGATGAT
 630 TTGGGAATG CCAGAGTCA TTTATGTCT CTCTACAGTG CATGTTCTC TGAGGTGCCA CATGGGCCAG TTGATCAGAA GTTTCATCC
 720 ATAGTATTG GCTGTGCTCT TGAAGATCAG AAGAAATTA AGAGAGATT AGAGACTCTG CTTAGAAATA TTGAAACTC TGACAGGCC
 810 ATCAGGCTAT TAGAGCATTG TAAGGAGCT GGTTCACAAA CTCTGCACAA AATGCTGAA AGCAGATTCA ATTAGTCTC AATCCTAGA
 I K L L E H S K G A G S K T L Q Q N A E S R F N

FIGURE 2B

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GCATTACAC AATACACACAG GTGTAAAAAT GATAAATATAC TATTTTAATT GATACTAGT TCTTTGTTAG GTATACCCAC TTAGTTGACA 900
CTGATAGTTG TTTCAGATGA GGAATATATT CCATCAGTA TCTTCAGTTT TGTGATATAC AAAACTAGCA ATATTTTAAAT TATCTATCTA 990
GAGATTTTTT AGATTGAATT CTTGTCTTGT ACTAGGATCT AGCATATTTT CACTATTCTGT GATGATATAC ATAGTTTGTG GGGAAAAACA 1080
ACGTTCAAGT AGGGGCAAAA AGCATGACTG CTTTTTCCTG TCTGGCATGG ATCACGCGAG TCACCTTGGG CATTTAGTTT ACTAGGAATT 1170
CTTACTGG
```

GCGAGCTCC R E L R	GORTCRAACC I Q P	CCGGGCGCG R A A	GCCACTTCT A N F S	CTGACTGGA G L D	CCAGAGTTT Q K F	CTAGCCGCC L A G Q	AGTTGCTACC L L P	TCCTTTATC P F I	90
TCCTCCTCC S S F P	CCTCTGCCAG S G S	CGAGGAGCT E E R	ATTTCAGAC I S R H	ACTTCCAGC F H P	CTCTCTGCC S L A	ACGTACCCC T S P P	CGCCTTTAT P L I	TCATAAGGT H K G	180
GCCCGCGCC R R R R	GGCTTCCCG H V G	ACAGCTCGG H U G	GGCGGAGGG G G E G	GGCCACGGC P T A	GGCGCCCGG A A R	CCAGAGACTC P E T R	GGCGCCCGA R P E	GCCAGCGCC P A P	270
CGACCCCGG R T R A	CCCAAGCGG P A G	CAGACCCCA R P Q	CCAGAGTGA P S H S	GGCCCGCAC A A T	CCACTCGCC H S P	ATGATGAGG H H Q U	TGGGCTCGG A S G	CACCGGTAC N G D	360
CGGAGCCCT R D P L	TGCCCCCGG P P G	ATGGGAGTC H E I	AAGATCAGC K I D P	CGAGAGCGG Q T G	CTGGCCCTC H P F	TTCTGGGAC F U D H	ACAGAGCGG H S R	CACCACTAG T T T	450
TGGAACGAC U N D P	CGCCCGTGC R U P	CTCTAGGGC S E G	CCCAAGGAG P K E T	CTCCATCCT P S S	TGCCAATGC A N G	CCTTCCCGG P S R E	AGGCTCTAG G S R	GCTGCCGCCT L P P	540
GCTAGGGAG R R E G	GCCACCTGT H P U	GTACCCCGA Y P Q	CTCCGACCA L R P G	GCTACATTCC Y I P	CATTCTCTG I P U	CTCCATGAG L H E G	GCGCTGAGA R E N	CCGGCAGGT R Q U	630
CACCCCTTT H P F R	ATGTCTATC U V P	CCAGCCCTGG Q P G	ATGCAGCGAT H Q R F	TCCGACTGA P T E	GGCGGAGCA A A A	CGGCTCCTC A A P Q	AGAGGTCCA R S Q	GTCACTCTG S P L	720
CGGGCGATG R G H P	CAGAACCCAC E T T	TACCCAGAT Q P D	AAACAGTGT K Q C G	GACAGGTGC Q U A	AGCGGCGCG A A A	GCAGCCGAC A A Q P	CCCAAGCCT P A S	CCAGGACCT H G P	810
GAGCGGTCC E R S Q	AGTCTCCAG S P A	TGCTCTGAC A S D	TGCTCATCT C S S S	CATCCTCCT S S S	GGCCAGCTG A S L	CCTTCTCTG P S S G	GCAGGAGCA R S S	CCTGGGAGT L G S	900
CACCACTCC H Q L P	CGCGGGGTA R G Y	CATCTCATT I S I	CCGCTGATC P U I H	ACGAGCAGA E Q N	CGTTACCCG U T R	CCAGCAGCC P A A Q	AGCCTCCTT P S F	CCACAAAGC H K A	990
CAGAGAGCG Q C T H	ACTACCCAC Y P A	GCAGAGGGT Q R G	GAGTACCAG E Y Q T	CCACCCAGC H Q P	TGTGTACCAC U Y H	AAGATCCAG K I Q G	GGGATGACT D D H	GGAGCCCCG E P R	1080
CCCTTCCGG P L R A	CGGCATCCCC A S P	GTTCAGGTCA F R S	TCTGTCCAG S U Q G	GTGCATCGA A S S	CCGGGAGGG R E G	TCCACAGCA S P A R	GGAGCAGCA S S T	GCCACTCCAC P L H	1170
TCCCTCTCG S P S P	CCATCCGTGT I R U	GCACCCGTG H T U	GTGCAGAGC U D R P	CTCAGCAGC Q Q P	CATGACCCAT H T H	CGAGAACTG R E T A	CACCTGTTT P U S	CCAGCCTGAR Q P E	1260
AAACAAACG N K P E	AAAGTAGCC S K P	AGGCCAGTT G P U	GGACCAAGC G P E L	TCCCTCCTG P P G	ACACATCCCA H I P	ATTCAAGTA I Q U I	TCCGCAAGA R K E	GGTGATTCT U D S	1350
AAACTGTGT K P U S	CCACAGAGC Q K P	CCACCTCCC P P P	TCTGAGAGG S E K U	TAGAGGTGA E U K	AGTTCCCCCT U P P	GCTCCAGTC A P U P	CTTGCTCTC C P P	TCCAGCCCT P S P	1440
GGCCTTCTG G P S A	CTGTCCCTC U P S	TCCCCAGAG S P K	AGTGTGGTA S U A T	CAGAGAGAG E E R	GGCAGCCCC A A P	AGCACTGCC S T A P	CTGCAGAGC A E A	TACACCTCA T P P	1530
AAACAGGAG K P G E	AGCCGAGGC A E R	TCCCCAGAA P P K	CATCCAGGAG H P G U	TGCTGAAGT L K U	GGAGGCCATC E A I	CTGCAGAGG L E K U	TGAGGGGCT Q G L	GGAGCAGCT E Q A	1620
GTAGACACT U D H F	TTCAGGCCAA E G K	GAGAGCTGAC K T D	AAAAAGTACC K K Y L	TGATGATCGA H I E	AGAGTATTTG E Y L	ACCAAGAGC T K E L	TGCTGGCCCT L A L	GGATTGAGT D S U	1710
GACCCCGAG D P E G	GACGAGCCGA R A D	TGTGCGTCAG U R Q	GCCAGGAGAG A R R D	ACGGTGTGAG G U A	GAGGTTTCAG K U Q	ACCATCTTGG T I L E	AAAAACTTGA K L E	ACGAGAGCC Q K A	1800
ATTGATGTCC I D U P	CAGGTCAAGT G Q U	CCAGGTCTAT Q U Y	GAACTCCAGC E L Q P	CCAGCAACT S H L	TGAGCAGAT E A D	CAGCCACTGC Q P L Q	AGGCATCAT A I H	GGAGATGGT E H G	1890
GCCCTGGCA A U R A	CAGAGACGG D K G	CAGAGAAAT K K H	GCTGAAATG A G H A	CAGAGATCC E A D P	CCACACGAA H T E	ATCCAGCAG T Q Q P	CAGAGCAAC E A A	AGCAGAGCG A A R	1980
ACTTCAAAAC T S H P	CCAGCAGCAT S S H	GACGACACCC T D T	CCTGGTAAC P G H P	CAGCAGCAC A A P	GTAGCCTCTG .	CCCTGTARAA .	GTGAGACTCG .	GAACCGATGT .	2070
GTGCTTTAG AAACTATA	GATTTTAGTT AGGGCTAAA	GATGCAATTT AGGGAAATG	CAGAGACTTT ATGCTTTTCT	AGGTGAGTTG TCAATATTCT	GTTTGTATTA TACTCTTGTA	GCTGCTTGGT CAATTAAGGA	ATGCACTACT AGTTGCTTGT	TGGTGAGGC TGTTTGAGAA	2160
GTTTAACCC GTGCTTGT	GTGCTTGT CTGAGCCCT	GTGCTTGT GTGCTTGT	GTGCTTGT GTGCTTGT	GTGCTTGT GTGCTTGT	GTGCTTGT GTGCTTGT	GTGCTTGT GTGCTTGT	GTGCTTGT GTGCTTGT	GTGCTTGT GTGCTTGT	2250
GAAGTGAAG GCTAGATGG	GATGCAATTT GATGCAATTT	GAAGTGAAG GATGCAATTT	GAAGTGAAG GATGCAATTT	GAAGTGAAG GATGCAATTT	GAAGTGAAG GATGCAATTT	GAAGTGAAG GATGCAATTT	GAAGTGAAG GATGCAATTT	GAAGTGAAG GATGCAATTT	2340
TGATCTCAT ATTAAATA	ATTAAATA CCTGACTTTA	ATTAAATA CCTGACTTTA	ATTAAATA CCTGACTTTA	ATTAAATA CCTGACTTTA	ATTAAATA CCTGACTTTA	ATTAAATA CCTGACTTTA	ATTAAATA CCTGACTTTA	ATTAAATA CCTGACTTTA	2430
ATTAAATA CCTGACTTTA	ATTAAATA CCTGACTTTA	ATTAAATA CCTGACTTTA	ATT						

90 ACATATCCT GTAGACCAC GATTGCAAG GCCAAGTTT GAATTCCTTAT ACAATGGAG CGTATGGTCC AACATACCCC CCAGGCCCTG
 180 GGGCAATAC TGCCTCATAC TCAGGGGCTT ATTATGCACC TGGTATACT CAGACCAGTT ACTCCACAGA AGTTCACAGT ACTTACCCTT
 270 CATCTGGCA CAGCCCACT CCAGTCTCTC GTTGGATCTA TCCCCAGCAG GACTGTCAAG ACTGAAGCAC CCCCTCTTAA GGGGCAAGTT
 360 CCAAGATATC CGCCTTCACA GACCCTGGA ATGACCCTGC CCATTATCC TTATGGAGAT GGTATCGTA GTGTCCACA ATCAGGCCG
 450 ACTATAGC CACAGGAAG ATGGTGGG TTCTCCTGGT GCTTATGGA TGGGTGGCG TTATCCCTGG CTTTCATCAG CGCCCTCAGC
 540 ACCACCGGC ATCTCTACA TACTGAAAG TACTTCACCA TGGCCTAGCA GTGGCTCTCC CCAATCAGCC CCTTCACCCC CAOTCCAGCA
 630 GCCAAGGAT TCTTCATACC CCTATAGCCA ATCAGATCAA AGCATGACC GGCACACTT TCCTTGCAGT GTCCATCAGT ACGATCCTC
 720 GGGACAGTG AACATGATG ATTCAGATCT TTGGATTCC CAGTCCAGT ATAGTGCTGA GCCTCAGCTG TATGGTATG CCACCAAGTGA
 810 CCATCCCAAC ATCAGATC AAGTAGCAG TCTTCTGGA GAATGTATC CTTCAGATGA AATGACTCCT CCGAGTATTA AAAAATCAT
 900 H P N N Q D Q S S L P E E C V P S D E S T P P S I K I I
 ACATGTGCTG GAGAGGTCC AGTATCTTGA ACAGAGTA GAGGATTG TAGGAAAAA GACAGACAAA GCATACCTGC TTCTGGAGA
 990 H V L E K V Q Y L E Q E V E E F V G K K T D K A Y W L L E E
 AATGCTAACC AAGGAACCTT TGGACTGGA TTCAGTTGAA ACTGGGGGCC AGGACTCTGT ACGGACGGCC AGAAAAGAGG CTGTTTGTAA
 1010 M L T K E L L E L D S V E T G G Q D S V R Q A R K E A U C K
 GATTCAGGCC ATATTGAAA
 I Q A I L E

FIGURE 5

90 GAGARATATAA AATGACTT CTCCAGGCAC AARCCCTTC TGATTGTAC CTGAGCTCCA AAGCAGATT GCAGGGTTTA ATTGACAGT
E I K N E L L Q A Q N P S E L Y L S S K T E L Q G L I G Q L
180 TGGATGAGT AAGTNTTGA AAAACCCCT GCATCCGGG AGCCAGAGCA AGAGCAGTGA TCGAGGTGCA AACTCTGATC ACATATATTG
D E U S X E K N P C I R E A R R R A U I E V Q T L I T Y I D
270 ACTTGAGGA GGCCTTGAG AAGAGAAAGC TGTTTGCTTG TGAGGAGCAC CCATCCCAT AAGCCGTCTG GAGCGTCTT GGAACCTTGT
L K E A L E K R K L F A C E E H P S H K A U W N U L G N L S
360 CTGAGATCCA GGGAGAGTT CTTTCATTTG ATGGAATCG AACCGATAAG AACTACATCC GGCTGAGAGA GCTGCTCACC AAGCAGCTGC
E I Q G E U L S F D G N R T D K N Y I R L E E L L T K Q L L
450 TAGCCCTGGA TGCTGTTGAT CCGCAGGGAG AAGAGAGTG TAGGCTGCC AGGAACCAAG CTGTGAGGCT TCGCAGAT ATTCTCAGCT
A L D A U D P Q G E E K C A A R K Q A U R L A Q N I L S Y
540 ATCTCAGCT GAATCTGAT GAATGGGAGT ACTGAATAC CAGAGATCTC ACTTTTGATA CTGTTTGA CTTCATATGT GCTTCTATGT
L D L K S D E W E Y
630 ATAGAGAGCT TTCAGTTCAT TGATTATAC GTGCATATTT CAGTCTCAGT ATTTATGATT GAGGCAATT CTATTCAGTA TCTGCTGCTT
689 TTGATGTTGC AAGACAATA TCATTACAGC AGGTTACTT TTCCATTCCG ATCAAAAA

FIGURE 6A

ATGTCCTTCCGCTCTTCGTTGAAATATTTCACTTTCTTTCCAGCTTTTCCCCATCTCGACCT
GCTTTGGTTTTT
CGAGAAAACCGTTCCAAATCAGCGACATCTCTCAAATTGAGATCATAGGCTTTTGAAGATTG
CTCAAATTATG
CTTCTCATATTGCATGAGCATTTTGAAGCCCGCGTCATCAACCAAAGCATTTTTTCCACCCATCA
CAATGATTTTAT CATTTCCTTTAAAATT

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FIGURE 6B

MKVNVCSSV	OTTIDILEEN	QGEDESILTL	GQLRDRIATD	NDVDVETMKL	50
LHRGKFLQGA	DDVSLSTLNF	KENDKIIVMG	GKNALVDDAG	FKMLMQYEKH	100
NLSNLQKAYD	LNLRDVADLE	RGFLEKPKQV	EMGKKLEKKV	KYFNEEAERH	150
LETLDGMNII	TETTPENQAK	RNREKRKTLV	NGIQTLNQN	DALLRRLQEY	200
QSVLNGDIPE					210

FIGURE 7A

ATGCCAGTCG	TGAACATACC	AATCAAAATA	CTTGGTCAGA	ATCAATCACA	50
TAGTCGAAGT	AACTCCTCGT	CTTCTGTTGA	CAACGATCGA	AATCAACCAC	100
CACAGCAGCC	ACCTCAACCG	CAACCACAAC	AGCAATCTCA	GCAACAATAC	150
CAGCAGGCTC	CAAACGTGAA	TACCAATATG	CATCATTTCCA	ACGGATTCTC	200
ACCTAACTTC	CCATCTCGTA	GTCCTATTCC	GGACTTTCCC	AGTTTTTCAT	250
CTGGGTTCCC	AAACGATTCT	GAATGGTCTT	CGAATTTCCC	GTCGTTTCCA	300
AATTTCCCAA	GTGGATTCTC	AAATGGAAGT	TCTAATTTCC	CTGATTTTCC	350
AAGATTCGGA	AGAGATGGAG	GACTATCGCC	AAACCCACCG	ATGCAAGGAT	400
ACAGGAGAAG	TCCAACACCA	ACATCAACTC	AATCTCCAAC	TTCTACATTA	450
AGACGCAACT	CTCAGCAGAA	TCAAGCTCCT	CCACAATATT	CTCAGCAACA	500
ACCACAACAA	GCTCAACAAC	GTCAGACAAC	TCCTCCGTCA	ACAAAAGCTT	550
CATCTCGACC	ACCATCTCGT	ACTCGTGAAC	CAAAGGAACC	TGAGGTACCC	600
GAGAGACCAG	CAGTTATTCC	ATTGCCATAT	GAGAAGAAGG	AGAAACCACT	650
GGAGAAGAAA	GGTAGTCGTG	ATTCTGGAAA	GGGTGATGAG	AACCTTGAAG	700
AGAACATTGC	CAAGATCACG	ATCGGAAAGA	ATAATTGCGA	GTTATGTCCG	750
GAACAAGAAA	CGGACGGCGA	CCCATCTCCA	CTAACCTCCC	CAATCACCGA	800
AGGAAAGCCA	AAGAGAGGAA	AGAAACTTCA	ACGTAATCAA	AGTGTTGTTG	850
ATTTCAATGC	CAAGACAATT	GTTACTTTGG	ATAAAATTGA	ATTACAAGTT	900
GAGCAGTTGA	GAAAAAAGC	TGCTGAACTC	GAAATGGAAA	AAGAGCAAAT	950
TCTTCGTTCT	CTAGGAGAAA	TCAGTGTTCA	TAACTGCATG	TTCAAACCTG	1000
AAGAATGTGA	TCGTGAAGAG	ATTGAAGCAA	TCACTGACCG	ATTGACAAAA	1050
AGAACAAAGA	CAGTTCAAGT	TGTTGTCGAA	ACTCCACGAA	ATGAAGAACA	1100
GAAAAAAGCA	CTGGAAGATG	CAACTTTGAT	GATCGATGAA	GTCGGAGAAA	1150
TGATGCATTTC	GAATATTGAA	AAGGCTAAGC	TGTGCCTACA	AACCTACATG	1200
AACGCCTGTT	CGTACGAAGA	AACTGCTGGA	GCCACCTGCC	AAAACCTCTT	1250
GAAGATCATA	ATTCAGTGCG	CTGCTGATGA	TCAGAAACGC	ATCAAGCGTC	1300
GTCTGGAAAA	TCTGATGTCT	CAAATTGAGA	ATGCTGAGAG	AACGAAAGCA	1350
GATTTGATGG	ATGATCAAAG	CGAATAG			1377

FIGURE 7B

MPVVNIPIKI	LGQNQSHSRS	NSSSSVDNDR	NQPPQQPPQP	QPQQQSQQQY	50
QQAPNVNTNM	HHSNGFSPNF	PSRSPIDFP	SFSSGFPNDS	EWSSNFPSFP	100
NFPSGFSNGS	SNFPDFPRFG	RDGGLSPNPP	MQGYRRSPTP	TSTQSPTSTL	150
RRNSQQNQAP	PQYSQQQPQQ	AQQRQTTPPS	TKASSRPPSR	TREPKEPEVP	200
ERPAVIPLPY	EKKEKPLEKK	GSRDSGKGDE	NLEENIAKIT	IGKNNCELCP	250
EQETDGDPS	LTSPITEGKP	KRGKKLQRNQ	SVVDFNAKTI	VTLDKIELQV	300
EQLRKKAEL	EMEKEQILRS	LGEISVHNCM	FKLEECDREE	IEAITDRLTK	350
RTKTVQVVVE	TPRNEEQKKA	LEDATLMIDE	VGEMMHSNIE	KAKLCLQTYM	400
NACSYEETAG	ATCQNFLKII	IQCAADDQKR	IKRRLENLMS	QIENAERTKA	450
DLMDDQSE					458

FIGURE 8A

ATGTCAGAAA	AGACTAGCAC	AGTTACAATA	CACTATGGAA	ATCAGCGATT	50
TCCGGTAGCA	GTCAATCTAA	ATGAGACGTT	AAGTGAACTG	ATTGATGATT	100
TACTTGAAAC	GACTGAGATT	TCTGAGAAGA	AAGTCAAGCT	TTTTTACGCT	150
GGCAAGCGTT	TAAAAGACAA	AAAAGCCTCG	TTATCAAAAT	TGGGTTTAAA	200
AAATCATAGT	AAAATTCTAT	GTATAAGACC	ACATAAGCAA	CAACGAGGTT	250
CCAAGGAAAA	AGACACGGTT	GAGCCCGCTC	CGAAAGCGGA	AGCGGAGAAT	300
CCTGTATTTT	CGCGTATTTT	TGGAGAAATA	AAAGCCATCG	ATCAGTATGT	350
TGACAAAGAA	CTTTCCCCCA	TGTACGACAA	TTACGTAAAT	AAACCGTCGA	400
ACGATCCAAA	GCAGAAAAAC	AAACAGAAAC	TAATGATAAG	TGAACTACTT	450
TTACAACAGC	TTTTAAAATT	GGATGGAGTT	GACGTACTGG	GCAGCGAGAA	500
ATTGCGTTTT	GAACGGAAGC	AACTTGTTTC	TAAGATCCAA	AAAATGTTTG	550
ATCACGTTGA	CCAAACAAGC	CAAGAAGTGG	CCGCATAG		588

FIGURE 8B

MSEKTSTVTI	HYGNQRFPA	VNLNETLSEL	IDDLLETTEI	SEKKVKLFYA	50
GKRLKDKKAS	LSKLGLKNHS	KILCIRPHKQ	QRGSKEKDTV	EPAPKAEAEEN	100
PVFSRISGEI	KAIDQYVDKE	LSPMYDNYVN	KPSNDPKQKN	KQKLMISELL	150
LQQLLKLDGV	DVLGSEKLRF	ERKQLVSKIQ	KMLDHVDQTS	QEVAA	195

FIGURE 9A

ATGTCTTTTT	TTACCCAGTT	GTGTTCTATG	GATAAAAAAT	ATTGGATCTC	50
TCTAGCTGTA	TTGTCAGTTA	CTGTTTGTGAT	TAGCGCATTA	TTGAAAAAGA	100
GAGCTACTGA	AACCGAAGAT	ATTGTCGTTG	TTCATTACGA	TGGCGAAAAG	150
TTGAATTTTG	TGTTGCGACA	ACCAAGGCTG	AATATGGTTT	CTTACACTAG	200
TTTTCTTCGT	CGCGTGTGCA	ACGCATTTTC	AGTAATGCCC	GACAAAGCGT	250
CTCTCAAGTT	AAACGGGGTG	ACCCTCAAGG	ATGGTTCACT	TTCCGACCAA	300
AATGTGCAAA	ATGGAAGTGA	ATTAGAGCTC	GAATTACCCA	AACTGAGCCC	350
GGCAATGCAA	CAAATTGAAG	CATATATAGA	TGAGCTTCAA	CAGGATCTCG	400
TCCCTAAAAT	TGAAGCCTTC	TGCCAATCGT	CTCCCGCTTC	GGCACAAGAT	450
GTTCAAGATT	TGCATACACG	CCTTAGTGAA	ACATTGTTGG	CTAGGATGAT	500
AAAATTAGAT	GCTGTTAATG	TTGAAGACGA	CCCAGAAGCT	CGTCTTAAAA	550
GAAAAGAAGC	TATTCGTTTA	TCTCAACAAT	ATTTGAGTAA	ACTAGATTCC	600
ACCAAGAATC	AAAACAAATG	A			621

FIGURE 9B

MSFFTQLCSM	DKKYWISLAV	LSVTVLISAL	LKKRATETED	IVVVHYDGEK	50
LNFVLRQPRL	NMVSYSFSLR	RVCNAFSVMP	DKASLKLVGV	TLKDGSLSLSDQ	100
NVQNGSELEL	ELPKLSPAMQ	QIEAYIDELQ	QDLVPKIEAF	CQSSPASAQD	150
VQDLHTRLSE	TLLARMIKLD	AVNVEDDPEA	RLKRKEAIRL	SQQYLSKLDS	200
TKNQNK					206

FIGURE 10A



FIGURE 10B

157 C K L D R R V K A T I I Q F M I L E E I I T I - I P E - - - - N F K I S R L K R K G L V K V Q A F I
 552 K K T D K K Y L M E E Y I T K E I L L D S V D P E G R A - - - - D V R Q A R H D G V R K V Q T I L
 167 K K T D K A Y W L L E E I I T K E I L L D S V D P E G R A - - - - S V R Q A R K E A V C K Q A I L
 79 N R T D K N Y I R L E E L L T K O L L L D A V D P Q E P E - - - - K C K A A R K Q A V R L A Q N I L
 134 C K L D R K V K A T I I Q F M I L E E I I T I - I P E - - - - Q F K L S R L K R K N L V K K V Q F I
 133 K K L R K K V K Y F N I E A E R L L E L L O L L K L D G V D V L G S E - - - - K H R F E R K K T L V N G Q T I L
 137 K K R N R K K L M S E L L O L L K L D A V N V E D D P - - - - K H R F E R K K T L V N G Q T I L
 145 R D V Q D L H T R L S I T L L A R I K L D A V N V E D D P - - - - K H R F E R K K T L V N G Q T I L
 164 L E D Q K K R R L I T L L R N E N S I K A I K I L E P H S K G A G S K U L Q Q T A E S - - - - R F N
 192 A D D Q K K R R L E N L U S Q I F A R I K I D L - - - - D D D S E

hBAG-1
 hBAG-3
 hBAG-4
 hBAG-5
 mBAG-1
 C.e BAG-1
 S.p BAG-1A
 S.p BAG-1B
 hBAG-2
 C.e BAG-2

FIGURE 11

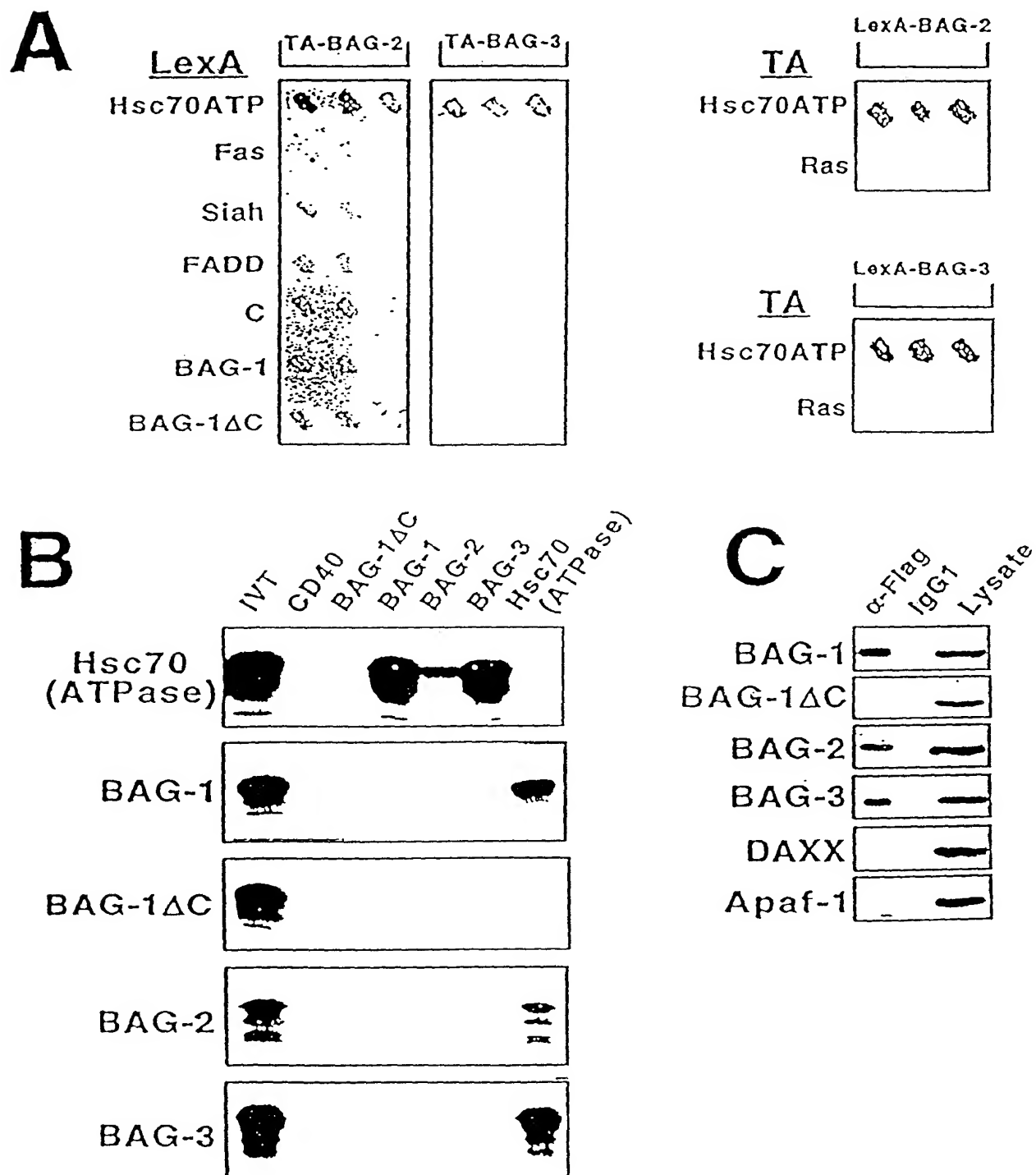


FIGURE 12

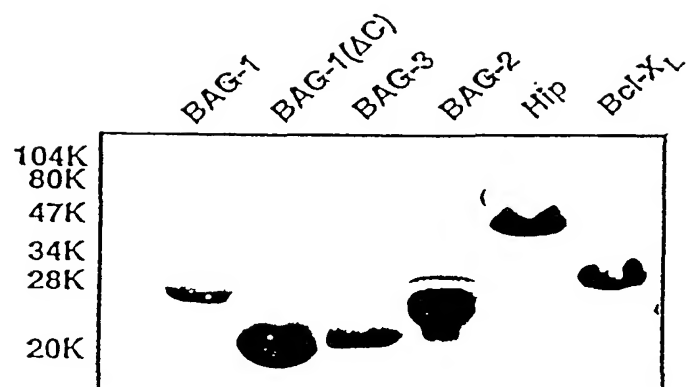


FIGURE 13

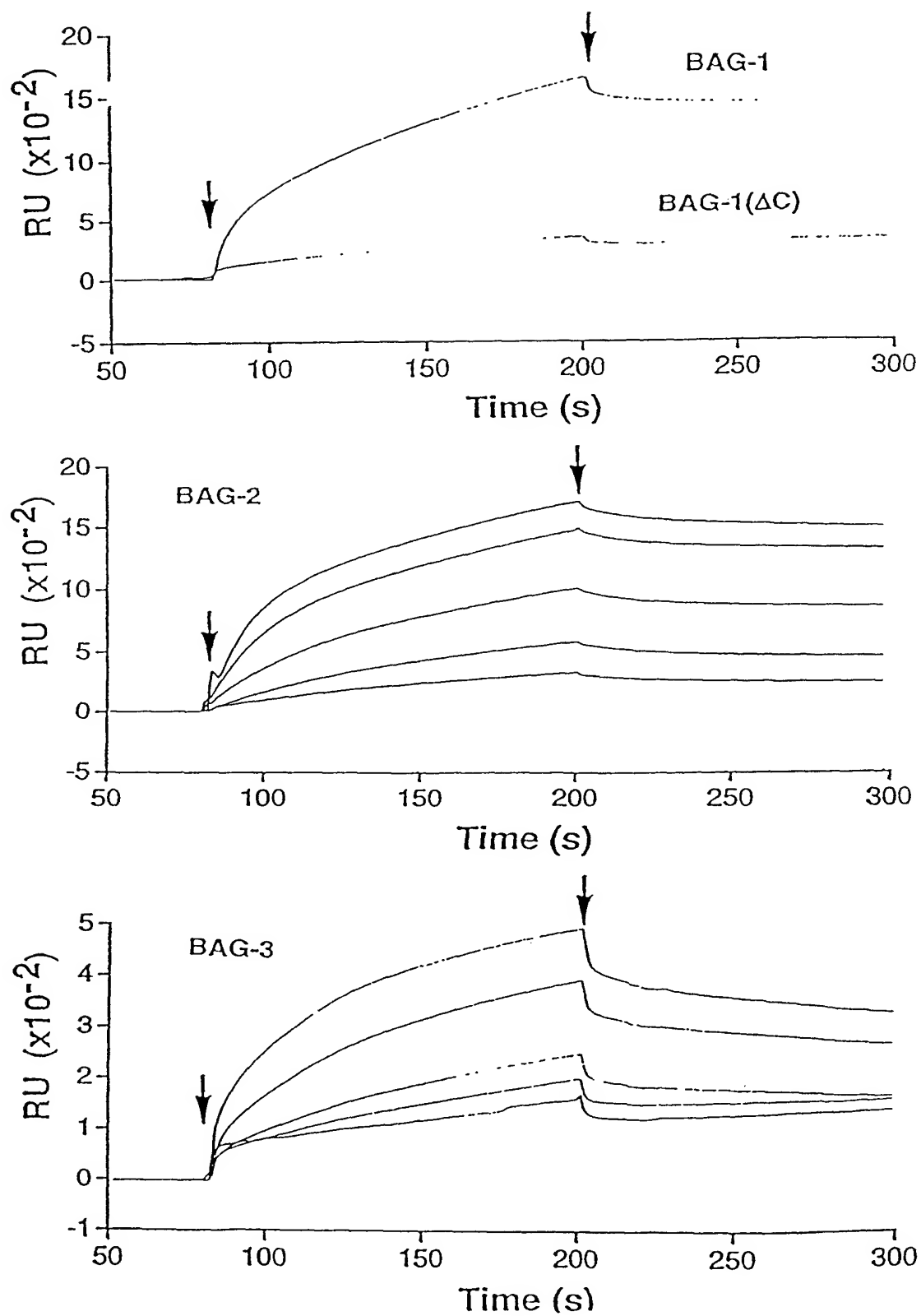


FIGURE 14

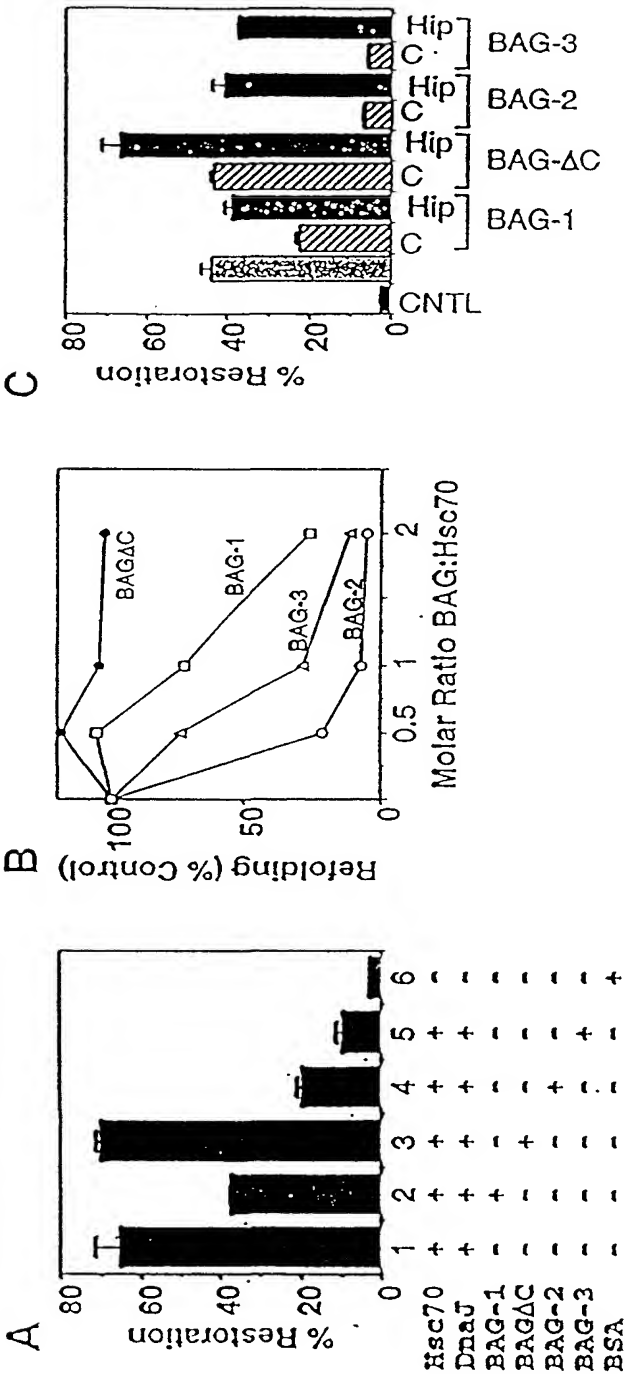


FIGURE 15A

GGGAGCTCC GCATCCAACC CCGGGCCGGG GCGAATTCT CTGGA CTGGA
50 CCAGAAGTTT CTAGCCGGCC AGTTGCTACC TCCCTTTATC TCCTCCTTCC
100 CCTCTGGCAG CGAGGAGGCT ATTTCCAGAC ACTTCCACCC CTCTCTGGCC
150 ACGTACCCC CGCCTTTAAT TCATAAAGT GCCGGGCGCC GGCTTCCCGG
200 ACAGTGGC GCGGAGAGG GCGCAAGGC GCGGCCCGG CCAGAGACTC
250 GCGCCCGGA GCGAGCGCC CGCAOCCGG CCGAGCGGG CAGACCCCAA
300 CCCAGCATGA GCGCGCCAC CCACTCGCC ATGATGCAGG TGGCGTCCGG
350 CAACGGTGAC CGCGACCTT TGCCCCCGG ATGGGAGATC AAGATCGACC
400 CGCAGACCG CTGGCCCTTC TCGTGGACC ACAACAGCCG CACCACTAG
450 TGGAACGACC CGCGGTGCC CTCTGAGGC CCGAAGGAGA CTCATCCTC
500 TGCCAATGGC CCTTCCGGG AGGCTCTAG GCTGCCGCT GCTAGGGAAG
550 GCCACCTGT GTACCCCGCAG CTCGACCCAG GCTACATTCC CATTCCTGTG
600 CTCCATGAAG GCGCTGAGAA CCGGCAGGTG CACCTTTCC ATGTCTATCC
650 CCAGCCTGG ATGCAGCGAT TCCGAATGA GCGGCAGCA GCGGCTCCTC
700 AGAGGTCCA GTCACCTCTG CCGGGCATGC CAGAAACCAC TCAGCCAGAT
750 AACAGTGTG GACAGGTGC AGCGCGGGC GCGGCCAGC CCGCAGCCTC
800 CCACGGACCT GAGCGGTCC AGTCTCCAG TGCCTCTGAC TGCTCATCCT
850 CATCCTCCTC GGCCAGCCTG CCTTCTCCG GCAGGAGCAG CCTGGGCAGT
900 CACAGCTCC CGCGGGGTA CATCTCCATT CCGGTGATAC ACGAGCAGAA
950 CGTTACCCGG CCAGCAGCC AGCCCTCCTT CCACAAAGCC CAGAAAGCAGC
1000 ACTACCCAGC GCAGAGGGT GAGTACCAGA CCGCAGCC TGTGTACCAC
1050 AAGATCCAGG GGGATGACTG GGAGCCCCG CCGTGGGG CGGCATCCCC
1100 GTTCAGGTCA TCTGTCCAGG GTGCATCGAG CCGGAGGGC TCACAGCCA
1150 GGAGCAGCAC GCCACTCCAC TCCCTCTGC CCATCCGTGT GCACACCGTG
1200 GTCGACAGGC CTCAGCAGCC CATGACCCAT CGAGAACTG CACCTGTTTC
1250 CCAGCCTGAA AACAAACCAG AAGTAAGCC AGGCCAGTT GGACCAGAAC
1300 TCCCTCCTGG ACACATCCCA ATTCAAGTGA TCCGCAAGA GTGGATTCT
1350

FIGURE 15A

AAACCTGTTT CCAGAAAGCC CCACCTCCC TCTGAGAAAG TAGAGGTGAA 1400
AGTCCCCCT GCTCCAGTTC CTTGTCTCTC TCCCAGCCCT GGCCCTTCTG 1450
CTGTCCCCTC TTCCCCCAAG AGTGTGGCTA CAGAAGAGAG GGCAGCCCCC 1500
AGCACTGCCC CTGCAGAAAG TACACCTCCA AAACCAGGAG AAGCCGAGGC 1550
TCCCCAAA CATCCAGGAG TGCTGAAAGT GGAAGCCATC CTGGAGAAAG 1600
TGCAGGGGCT GGAGCAGGCT GTAGACAACT TTGAAGGCAA GAAGACTGAC 1650
AAAAAGTACC TGATGATCGA AGAGTATTTG ACCAAAGAGC TGCTGGCCCT 1700
GGATTCAGTG GACCCGAGG GACGAGCCGA TGTGCGTCAG GCCAGGAGAG 1750
ACGGTGTGAG GAAGGTTGAG ACCATCTTGG AAAAATTGA ACAGAAAGCC 1800
ATTGATGTCC CAGGTCAAGT CCAGGTCTAT GAACTCCAGC CCAGCAACCT 1850
TGAAGCAGAT CAGCCACTGC AGGCAATCAT GGAGATGGGT GCCGTGGCAG 1900
CAGACAAAGG CAAGAAAAAT GCTGGAAATG CAGAAGATCC CCACACAGAA 1950
ACCCAGCAGC CAGAAAGCCAC AGCAGCAGCG ACTTCAAACC CCAGCAGCAT 2000
GACAGACACC CCTGGTAACC CAGCAGCACC GTAGCCTCTG CCCTGTAAAA 2050
ATCAGACTCG GAACCGATGT GTGCTTTAGG GAATTTTAAG TTGCATGCAT 2100
TTCAGAGACT TTAAGTCAGT TGGTTTTTAT TAGCTGCTTG GTATGCAGTA 2150
ACTTGGGTGG AGGCAAAACA CTAATAAAAG GGCTAAAAAG GAAAATGATG 2200
CTTTTCTTCT ATATTCTTAC TCTGTACAAA TAAAGAAGTT GCTTGTGTT 2250
TGAGAAGTTT AACCCCGTTG CTTGTTCTGC AGCCCTGTCT ACTTGGGCAC 2300
CCCCACCACC TGTTAGCTGT GGTGTGTCAC TGTCTTTTGT AGCTCTGGAC 2350
TGGAGGGGTA GATGGGGAGT CAATTACCCA TCACATAAAT ATGAAACATT 2400
TATCAGAAAT GTTGCCATTT TAATGAGATG ATTTTCTTCA TCTCATAATT 2450
AAAATACCTG ACTTTAGAGA GAGTAAAATG TGCCAGGAGC CATAGGAATA 2500
TCTGTATGTT GGATGACTTT AATGCTACAT TTTC 2534

FIGURE 15B

MSAATHSPMM QVASNGDRD PLPPGWEIK DPQTGWPFV DHNSRTTWN 50
DPRVSEGPKE TTPSSANGPS REGSRLPPAR EGHVPVQLR PGYIPVLH 100
EGAENRQVHP FHVYPQGMQ RFRTEAAAA PQRSQSPLRG MPETTQPKQ 150
CGQVAAAAA QPPASHGPER SQSPAASDCS SSSSSASLPS SGRSSLGSHQ 200
LPRGYISIPV IHEQNVTRPA AQPSFHKAQK THYPAQRGEY QTHQPVYHKI 250
QGDDWEPRPL RAASPFRRSS QGASSREGSP ARSSTPLHSP SPIRVHTVVD 300
RPQQPMTHRE TAPVSQLPEN PESKPGPVGP ELPPGHIPIQ VIRKEVDSKP 350
VSQKPPPPSE KVEVKVPPAP VPCPPPPSPGP SAVPSSPKSV ATEERAAPST 400
APAEATPPKP GEAEAPPKHP GVLKVEAILE KVQGLEQAVD NFEKKTKDKK 450
YLMIEEYLT ELLALDSVDP EGRADVROAR RDGVRKVQTI LEKLEQKAI 500
VPGQVQVYEL QPSNLEADQP LQAIMEMGAV AADKGKKNAG NAEDPHTETQ 550
QPEATAAATS NPSSMTDTPG NPAAP 575

FIGURE 15C

CCGAGCTCC GCATCCAGC CCGGCGCGC GCGACTTCT CTGACTGGA CCGAGACTTT CTHGCGGCG AGTTGCTHCC TCGCTTHTC 90
 TCTCTCTTC CTTCTGCGC CGAGGAGCT ATTCCAGAC ACTTCAGCC CTCTCTGCG AGTCCAGCC CCGCTTTHAT TCTHAGGCT 180
 CCGCGCGCC CCGTTCCGC ACAGCTCGC CCGCGAGAG GCGCCAGCC GCGCGCGCG CCGAGACTT CCGCGCGCG CCGAGCGCC 270
 CCGAGCGCG CCGAGCGCG CAGACCGCA CCGAGCTCA GCGCGCGCG CCGCTCGCC ATGATCGAG TCGCTCGCG CAGCGCTGAC 340
 H S A A T E S F M H Q V A S G H G J
 CCGAGCTTT TCGCGCGCG ATCGAGACT AGATCGAGC CCGAGAGCG CTGCGCTTC TTCTCGAGC AGAGAGCGC CAGCGCTHCG 450
 R D L F F G W E I K I D D Q T G W F I F V D E H S R T T T
 TCGAGCGAG CCGCGCTTC CTCTGAGCG CCGAGAGCA CTGATCTC TCGGATGCG CTTGCGCGC AGCGCTHAG CTTGCGCTT 540
 W H D D R V F S E G F K E T F S S A H G F S R I G S R L F F
 CTHGCGGAG CCGAGCTTT CTHGCGGAG CTGCGAGAG CTHGCTTC CATCTCTC CTGCTHAG CCGCTHAG CCGCGAGCT 630
 A R I G K F V Y F Q L R F G Y I F I F V L E E G A E H R Q V
 CAGCTTTTC ATCTCTHCC CCGCGCTTC ATCGAGGAT TCGAGACTA CCGCGAGCA CCGCGCTTC AGAGCTTCA CTGCTCTC 720
 K F I K V Y F Q F G M Q R I R T E A A A A A F Q R S Q S F L
 CCGCGCTTC CAGAGAGCG TCGAGGAT AAGAGCTC CAGAGCTG CCGCGCGCG CCGCGCGCG CCGAGCTTC CAGCGACTT 810
 R G H F I T T Q F D K Q C G Q V A A A A A A Q F Z A S E G F
 CAGCGCTTC ATCTCGAGC TCGCTHAG TCTGATCT CATCTCTC CCGAGCTTC CTTGCTGCG CAGAGAGAG CTTGCGACT 900
 I R S Q S F A A S D C S S S S S S A S L F S S G R S S L G S
 CAGAGCTTC CCGCGGCTH CATCTGAT CCGCTHAG CAGAGAGCA CTHGCGGCG CCGAGAGCG AGCGCTTCT CAGAGAGCG 990
 K Q L F R G Y I S I F V I E I Q H V T R F A A Q F S F E K A
 CAGAGAGCG ACTHCGAG CAGAGGCT CAGHCGAG CCGAGAGCG TCTHCGAG AGATCGAG CCGAGACT CAGCGCGCG 1080
 Q K T E Y F A Q R G I Y Q T E Q F V Y E K I Q G D W I F R
 CCGCTCGCG CCGCTCGCG CTGAGCTH TCTGAGAG CTHGCTGAG CCGAGAGCG TCGAGAGCA CAGAGAGCG CCGAGCTGAG 1170
 F L R A A S F I R S S V Q G A S S R E G S F A R S S T F L E
 TCGCTGCG CCGCTGCTT CAGAGCTTC CTHGAGCG CTHGAGCG CAGAGGCT CAGAGACT CAGCTTTC CAGCTTCA 1260
 S Z S F I R V E T V V D R F Q Q F M T E R I T A F V S Q F I
 AAGAGAGCG AAGCTHAG AGCGGCTT GAGAGAGAG TCGCTGCG CAGAGCTCA ATTGAGCT TCGAGAGCA CCGAGCTT 1350
 H K F I S K F G F V G F E L F F G E I F I Q V I R K I V D S
 AAGCTTTT CAGAGAGCG CCGAGCTTC TCTGAGAG TCGAGTGA AGTTCGCTT CTHGAGCT CTHGCTGCG TCGAGCTTC 1440
 K F V S Q K F F F F S I K V I V K V F F A F V F C F F F S F
 CCGCTTTC CTCTGCTTC TTGCGGAG ACTHCGCT CAGAGAGAG CCGAGCGCG AGCGCTGCG CTGAGAGCG TCGAGTGA 1530
 G F S A V F S S F K S V A T I E R A A F S T A F A I A T F F
 AAGAGAGCG AGCGGAGCG TCGCGGAG CTHGAGAG TCGAGACT CAGAGAGCG TCGAGAGCG TCGAGGCT CAGAGGCT 1620
 K F G I A I A F F K E F G V L K V I A I L I K V Q G L I Q A
 CTHGAGCT TTGAGAGCA CAGAGCTC AAGAGCTH TCTHCTGA AGCTHCTT CAGAGAGCG TCGCGCTT CAGAGCTT 1710
 V D H I I G K K T D K K Y L H I I I Y L T K E L L A F D S V
 CAGCGGAG CAGAGAGCG TCTGCTGAG CCGAGAGAG AGCTGCTG CAGAGCTC AGCTGCTT AAGAGCTH CAGAGAGCG 1800
 D F I G R A D V R Q A R R D G V R K V Q T I L I K L I Q K A
 ATTGCTTC CAGAGACT CCGCTHCT CAGCTGAG CAGAGACT TCGAGAGCT CAGAGCTT AGCGCTT CAGAGCTT 1890
 I D V F G Q V Q V Y I L Q F S K L I A D Q F L Q A I M E H G
 CCGCTGCG CAGAGAGCG CAGAGACT CTHGAGCT CAGAGCTC CAGAGAGCG AGCGGAGCG CAGAGAGCG AGCGGAGCG 1980
 A V A A D K G K K H A G H A I D F E T I T Q Q F I A T A A A
 ACTHAGAG CAGAGAGCT CAGAGAGCG CTHGAGCG CAGAGAGCG CTHGCTTC CCGCTHAG ATTGAGCT CAGAGCTT 2070
 T S H F S S H T D T F G H F A F F
 CTHGCTTC CAGAGCTT TCGAGCTT TCGAGCTT TCGAGCTT TCGCTHCT TCGCTHCT CTHGAGCT ACTHCTTC 2160
 AGCGGAGCG CTHGAGCT CCGAGAGCG CAGAGACT CTHGCTTC AGCTHCTT TCGAGAGCG TCGAGAGCT CTHGCTTC 2250
 TCGAGAGCT AGCGGCTTC CTHGCTTC AGCTHCTT ACTHCTTC CCGAGAGCG TCGAGCTT CTHGCTTC TCGCTHCT 2340
 AGCTHCTTC TCGAGAGCT CTHGAGCT CAGAGCTC TCGAGAGCT AGCGGAGCT TCGAGAGCT CTHGAGCT CTHGAGCT 2430
 ATTGCTTC TCGAGACT AAGAGCTC ACTHAGAG CAGAGAGCT TCGAGAGCG CTHGAGCT TCGCTHCT CTHGAGCT 2520
 ATTGCTTC TCGAGACT AAGAGCTC ACTHAGAG CAGAGAGCT TCGAGAGCG CTHGAGCT TCGCTHCT CTHGAGCT 2610
 ATTGCTTC TCGAGACT AAGAGCTC ACTHAGAG CAGAGAGCT TCGAGAGCG CTHGAGCT TCGCTHCT CTHGAGCT 2700

FIGURE 16A

CGGTGGAGCGGGGCGGGAA GCGCTTCAGG GCAGCGGATC CCATGTGCGC 50
CCTGAGGCGC TCGGGCTACG GCCCCAGTGA CGGTCCGTCC TACGGCCGCT 100
ACTACGGGCC TGGGGGTGA GATGTGCCG TACACCCACC TCCACCCCTTA 150
TATCCTCTTC GGCCTGAACC TCCCCAGCCT CCAATTCCT GCGGGGTGCG 200
CGGGGCGGCGCGGCGGAGA CCACCTGGCT GGGAGAAGGC GGAGGAGGCG 250
ATGGCTACTA TCCCTCGGGA GCGGCCTGGC CAGAGCCTGG TCGAGCCGGA 300
GGAAGCCACC AGGAGCAGCC ACCATATCCT AGCTACAATT CTAACATATTG 350
GAATTCTACT GCGAGATCTA GGGCTCCTTA CCCAAGTACA TATCCTGTAA 400
GACCAGAAAT GCAAGGCCAG AGTTTGAAT CTTATACAAA TGGAGCGTAT 450
GGTCCAACAT ACCCCCCAGG CCCTGGGGCA AATACTGCCT CATACTCAGG 500
GGCTTATTAT GCACCTGGTT ATACTCAGAC CAGTTACTCC ACAGAAGTTC 550
CAAGTACTTA CCGTTCATCT GGCAACAGCC CAACTCCAGT CTCTCGTTGG 600
ATCTATCCCC AGCAGGACTG TCAGACTGAA GCACCCCCCTC TTAGGGGGCA 650
GGTTCAGGA TATCCGCCTT CACAGAACCC TGAATGACC CTGCCCCATT 700
ATCCTTATGG AGATGGTAAT CGTAGTGTT CACAATCAGG ACCGACTGTA 750
CGACCACAAG AAGATGCGTG GGCTTCTCCT GGTGCTTATG GAATGGGTGG 800
CCGTTATCCC TGGCCTTCAT CAGCGCCCTC AGCACCCACC GGCAATCTCT 850
ACATGACTGA AAGTACTTCA CCATGGCCTA GCAGTGGCTC TCCCCAGTCA 900
CCCCCTTCA CCCCAGTCCA GCAGCCCAAG GATTCTTCAT ACCCCTATAG 950
CCAATCAGAT CAAAGCATGA ACCGGCACAA CTTTCCTTGC AGTGTCATC 1000
AGTACGAATC CTCGGGGACA GTGATCAATG AAGATTCAGA TCTTTTGGAT 1050
TCCCAAGTCC AGTATAGTGC TGAGCCTCAG CTGTATGGTA ATGCCACCAG 1100
TGACCATCCC AACAAATCAAG ATCAAAGTAG CAGTCTTCCT GAAGAATGTG 1150
TACCTTCAGA TGAAAGTACT CCTCCGAGTA TTAATAAAT CATACATGTG 1200
CTGGAGAAGG TCCAGTATCT TGAACAAGAA GTAGAAGAA TTGTAGGAAA 1250
AAAGACAGAC AAAGCATACT GGCTTCTGGA AGAAATGCTA ACCAAGGAAC 1300

FIGURE 16A

TTTTGAACT GGATTCAGTT GAAACTGGGG GCCAGGACTC TGACGGCAG 1350
GCCAGAAAAG AGGCTGTTTG TAAGATTCAG GCCATACTGG AAAAATTAGA 1400
AAAAAAAGGA TTATGAAAGG ATTTAGAACA AAGTGGAAGC CTGTTACTAA 1450
CTTGACCAA GAACACTTGA TTAGGTTAAT TACCCTCTTT TTGAAATGCC 1500
TGTTGATGAC AAGAAGCAAT ACATTCACGC TTTTCCTTTG ATTTTATACT 1550
TGAAAACTG GCAAAGGAAT GGAAGAATAT TTTAGTCATG AAGTTGTTTT 1600
CAGTTTTCAGA CGAATGAATG TAATAGGAA CTATGGAGTT ACCAATATTG 1650
CCAAGTAGAC TCACTCCTTA AAAAATTTAT GGATATCTAC AAGCTGCTTA 1700
TTACCAGCAG GAGGGAACA CACTTCACAC AACAGGCTTA TCAGAAACCT 1750
ACCAGATGAA ACTGGATATA ATTTGAGACA AACAGGATGT GTTTTTTTAA 1800
ACATCTGGAT ATCTTGTCAC ATTTTGTAC ATTGIGACTG CTTTCAACAT 1850
ATACTTCATG TGTAAATTATA GCTTAGACTT TAGCCTTCTT GGACTTCTGT 1900
TTTGTTTTGT TATTTGCAGT TTACAAATAT AGTATTATTCTCTAAAAA 1950
AAAAA AAAA 1966

FIGURE 16B

MSALRRSGYGPSDGYGRYGGGGDVVHPPPLVPLRPEPPQPPISWVRGGGPAETTWLGEGGGDGYPSGGAWP
EPGRAGGSHQEQPPYPSYNSNYWNSTARAPYPSYVVRPELQQSLNSYTNNGAYGPTYPPGPGANTASYSGAYYAPGY
TQTSYSTEVSTYRSSGNSPTVSRWYQQDCCQTEAPLRGQVPGYPPSQNPGMTLPHYPYGDGNRSVPQSGPTVRPQE
DAWASPGAYGMGGRYFPWPSSAPSPGNYMTTESTSPWPSSGSPQSPSPVQQPKDSSYPYQSDDQSMNRHNFPCSVHQ
YESSGTVINEDSDLLDSQVQYSAEPQLYGNATSDHPNNQDQSSSLPEECVPSDESTPPSIKKIHHVLEKVQYLEQEVEEF
VGKKTDKAYWILLEMLTKELLELDVETGGQDSVRQARKEAVCKIQAIKLEKKGL

FIGURE 16C

CCTTCCAGC GGGGCGGAA GCGCTTCAOC CCAGCGGATCCCATGTGCGC CCTGAGCGCC TCGGCTACG GCGCCAGTGA CGGTCCCTCC 90
 H S A L K R S G Y G P S D G P S
 TACCCCGCT ACTACGCGC TCGGCTGGA GATGTGCGG TACACCCACC TCCACCTTA TATCCTCTTCGCGCCCTGAACC TCCCGAGCCT 160
 Y G R Y Y G P G G G D V P V H P P P L Y P L R P E P P O P
 CCGATTTCCT GCGCGGTGCG CCGCGCGCC CCGCGCCACA CCACTCTGCT GCGAGAGCC CGAGGAGCGCA TCGCTACTA TCCCTCGGGA 270
 P I S W R V R G G G P A E T T W L G E G G G C D O Y Y P S G
 CGCGCTGCG CAGAGCTCG TCGAGCGGAGGAGGCCACAGAGAGCC ACCATACTCTAGCTACAA TCTAACTATG GAATTCTACT 360
 G A W F E P G R A G G S H Q E Q P P Y P S Y N B N Y W M S T
 CCGAATCTTA GCGCTCCTTA CCGAAGTACA TATCTCTTAAGACCCAGATT GCAAGCCACAGCTTGAATTCTTATACAAA TCGAGCCTAT 450
 A R S R A P Y P S T Y P V R P E L Q G Q S L N S Y T N G A Y
 GGTCCAACTATACCCCGCAOC CGCTGGGCAAA TACTGCTCATACTAGCGGCTTAT TATGCACTCGTTATACTACAGAC CAGTTACTCC 540
 G P T Y P F C P G A N T A S Y S G A Y Y A P G Y T Q T S Y S
 ACAGAACTTC CACTACTTA CCGTTCACTCTGGCAACAGCCCACTCCAGTCTCTCTGTGGATCTATCCCCAGCAGACTCTCAGACTGAA 630
 T E V P S T Y R S S G E S P T P V S R W I Y P Q Q D C Q T E
 GCACCCCCTT TAGCGGCA CCGTTCCAGGA TATCCGCTTCA CAGAAACCTCCAA TCGCCCTGCGCCATTATCTTATGAGATGCTAAT 720
 A P P L R C Q V P G Y P P S Q N F G M T L P H Y P Y G D G N
 CGTAGTGTTC CACAAACAG ACGGACTGTA CGACCAAGAGAGATCGTC GCGCTTCTCTCTGCTCTATGGAATGGTGG CCGCTTATCCC 810
 R S V P Q S G P T V R P Q E D A W A S P G A Y C M G K R Y P
 TGGCTTCAT CAGCGGCTC AGCAACACCGGCAATCTCTACATGACTGAAAGTACTTCA CCAATGGCTAGCAGTGGCTCTCCCGAGTCA 900
 W P S S A P S A P P Q N L Y M T E S T S P W F S S G S P Q S
 CCGCTTCAC CCGCAGTCCA GCGCGCCAGGATTCTTCA TACCCCTATAG CCAATCAGATCAAGCATGAACCGGCAAACTTTCTCTGC 990
 P P S P P V Q Q P K D E S Y P Y S Q S D Q S M N R H N F P C
 AGTTTCCATC AGTACCAATC CTCCCGACACTGAACAA TGAAGATTGAGA TCTTTTGGATTCGCCAAGTCCAGTATAGTGC TGAAGCTCAG 1080
 S P R Q Y E S S G T V N M E D S D L L D S Q V Q Y S A E P Q
 CTGTATGGTAATGCCACAG TGCCTA TCCAAATCAAGATCAAGTAG CAGTCTTCTCTGAAGAA TGTGTACCTTCAGATGAAGTACT 1170
 L Y G N A T S D H F M H Q D Q S S S L P E E C V P S D E S T
 CCTCCAGTAT TAAAAAAT CATACATGTG CTGAGAAAGGTC CACTATCTTCACAAAGATAGAGAA TTTGTAGAAAAAAGACAGAC 1260
 R P S I K K I I R V L E K V Q Y L E Q R V E E F V G K K T D
 AAAGCATACTGGCTTCTGAAAGAA TGTAAACCAAGGAAC TTTTGGAACTGGATTCA GTTGAAACTGGGCGGAGGCTCTGTACGGCAG 1350
 K A Y W L L E E H L T K E L L E L D S V E T G G Q D S V R Q
 GCGAGAAAGAGCGCTCTTTG TAAGATTGAGGCCATCTGGA AAAATTAGAAAAAAGGATTATCA AAGGATTATGACAAAGTGGAGC 1440
 A R K E A V C K I Q A I L E K L E K K G L .
 CTGTACTAATCTGACCAAGAACACTTGA TTAGTTAATTA CCGCTCTTTTGGAAATGCC TGTGATGACAAAGCAATACATTCCAGC 1530
 TTTTCTTTGATTTATACCTTGA AAACTGCAAGGAATGGAGAA TATTTAGTCAATGAAGTTATTTTCAGTTTTCAGAGCAATGAAT 1620
 GTAA TAGAACTATGGATTACCAATATTCGCACTACA CTACTCTTAAAAAATTTATGGATATCTACAAAGCTGCTTATTAACAACA 1710
 GGAAGGAACACACTTCACAAAGCGCTTATCAAAA CCAACAGATGAAGTGGATA TAAATTGAGACAAAAGGATGTGTTT TTA 1800
 AACACTGGA TATCTGTCA CATT TTTGTACATGTCACTCTCTTCAACA TATACTTCA TGTATAATTA TACTTAGACTTTAGCGCTCT 1890
 TGCATCTCTCTTTTGTGTTTGTATTTGCA GTTTCAAATATAGTATTAATCTCT 1946

FIGURE 17A

CCCCCCCC CCCCCCCCC CCNGAAGAG CCGGAGCGG CTGCTGCAGC 50
CAGTAGCGG CCTTCACCG GCTGCCCCG TCAGACCTAG TCGGAGGGG 100
TGGAGGCAT GCAGCTGGG GCCAGCTCC GGTGCCGCAC CCGTAAAGG 150
GCTGATCTC CACCTCGCA CTCAGCCAC GGGAGGCCA GACCGCATCC 200
AATCAGACT TCTTTTGGT CTTGTGAAAC TGAACACAAC AAAAGTATGG 250
ATATGGGAA CCAACATCCT TCTATTAGTA GGCTTCAGGA AATCCAAAAG 300
GAAGTAAAA GTGTAGAACA GCAAGTTATC GGCTTCAGTG GTCTGTCAGA 350
TGACAAGAAT TACAAGAAAC TGGAGAGGAT TCTAACAAAA CAGCTTTTGG 400
AAATAGACTC TGATAGATACT GAAGGAAAAAG GAGATATTCA GCAAGCTAGG 450
AAGCGGCAG CACAGGAGAC AGAAGTCTT CTCAAAGAGT TGGAGCAGAA 500
TGCAAAACCAC CCACACCGGA TTGAAATACA GAACATTTTT GAGGAAGCCC 550
AGTCCCTCGT GAGAGAGAA ATTGTGCCAT TTTATAATGG AGGCAACTGC 600
GTAACCTGATG AGTTTGAAGA AGGCATCCAA GATATCATTG TGAGGCTGAC 650
ACATGTTAAA ACTGGAGGAA AAATCTCCTT GCGGAAAGCA AGGTATCACA 700
CTTTAACCAA AATCTGTGCG GTGCAAGAGA TAATCGAAGA CTGCATGAAA 750
AAGCAGCCTT CCCTGCGCT TCCGAGGAT GCACATCCTT CCGTTGCCAA 800
AATCAACTTC GTGATGTGTG AGGTGAACAA GCGCCGAGGG GTCCTGATTG 850
CACTTCTGAT GGGTGTGAAC AACAATGAGA CCTGCAGGCA CTTATCCTGT 900
GTGCTCTCGG GGCTGATCGC TGACCTGGAT GCTCTAGATG TGTGCGGCCG 950
GACAGAAATC AGAAATTATC GGAGGGAGGT AGTAGAAGAT ATCAACAAAT 1000
TATTGAAATA TCTGGATTGG GAAGAGGAG CAGACACAAC TAAAGCATTT 1050
GACCTGAGAC AGAATCATTG CATTTTAAAA ATAGAAAAGG TCCTCAAGAG 1100
AATGAGAGAA ATAAAAATG AACTTCTCCA AGCACAAAAC CCTTCTGAAT 1150
TGTAACCTGAG CTCGAAAACA GAATTGCAGG GTTTAATTGG ACAGTTGGAT 1200
GAGGTAAGTC TTGAAAAAA CCCCTGCATC CCGGAAAGCCA GGAGAAAGAGC 1250
AGTGATCGAG GTGCAAACTC TGATCACATA TATTGACTTG AAGGAGGCC 1300

FIGURE 17A

TTGAGAAAAG AAAGCTGTTT GCTTGTGAGG AGCACCCATC CCATAAGCC 1350
GTCTGGAACG TCCTTGGAAA CTTGTCTGAG ATCCAGGGAG AAGTTC TTTC 1400
ATTTGATGGA AATCGAACCG ATAAGAACTA CATCCGGCTG GAAGAGCTGC 1450
TCACCAAGCA GCTGCTAGCC CTGGATGCTG TTGATCCGCA GGGAGAAGAG 1500
AAGTGTAAGG CTGCCAGGAA ACAAGCTGTG AGGCTTGCGC AGAATATTCT 1550
CAGCTATCTC GACCTGAAAT CTGATGAATG GGAGTACTGA AATACCAGAG 1600
ATCTCACTTT TGATACTGTT TTGCAC TTCA TATGTGCTTC TATGTATAGA 1650
GAGCTTTTCAG TTCATTGATT TATACGTGCA TATTTCAAGTC TCAGTATTTA 1700
TGATTGAAGC AAATTCTATT CAGTATCTGC TGC TTTTGAT GTTGCAAGAC 1750
AAATATCATT ACAGCACGTT AACTTTTCCA TTCGGATCAT TATCTGTATG 1800
ATGTGGTGTG GTTTGTTTGG TTTGTCTCTT TTTTGCGTT TTTAATCAGA 1850
AAACAAAATA GAGGCAGCTT TTGTAGATTT TAAATGGGT GTGCAAGCAT 1900
TAAATGCAG GTC TTTTCAGA ATCTAGAACT AGGCATAACC TTACATAATA 1950
CTAGGAAAAT TATGAGAAAG GGGAAATTTT TGGTTAAATA AGAGTAAAGT 2000
TCAAACACAA GCAGTACATG TTCTGTTTCA TTATGCTCGA TAGAAGGCTT 2050
TTTTTTCAC TATAAGGCCT GATTGGTCTT ACCCAGCTTA ACGGGTGCG 2100
GTTTTTTTGT TTGTTTCAGC AGTCTGTTCT TTTGTAAACA TTTTGTAGTTG 2150
GAAAAACAGC ATCTGCATTT TCCCCATCCT CTACGTTTTA GAGAGGAATC 2200
TTGTTTTTGT GTGCAACATA AGAAAAATTAT GAAACTAAT AGCCAAAAA 2250
CCTTTGAGAT TGCATTAAAG AGAAGGGATA AAGGACCAGC AATAATACCT 2300
TGTAAGTTGC TTTTGT TTTGT AAAATCTGAG CTTATAGTTT TCCTTAGTGA 2350
GTAAATTCAT AAGGATGGGA ACATTTAAAT TAAGTTAATG GGCCTTTAAA 2400
AAAAAAAAG GAAACACTCA TACCTGTAGT TGGAGGATGA ATACTGGAGA 2450
CGGGTTACCA ATGTCAGGTT ATACTAAAAC TAAATCAGAA AGTCTGAATG 2500
TAGCACATAA TGGTTCTCTT CTGTTGTCCA AGGCTGTAAA ATGGACAGCC 2550
TTGTCACACC TCCCGGTGTC TGTTTTACAA CGTGAGGGTA GACGCTGTCA 2600

FIGURE 17A

GTAACCCAGA GGGACCAGGC CTTCTAGGT TTTCTAGGCA GTCAGCTGTT 2650
AACCACTCAC TTAGTAAATG TCATAACTAC ACCTGCTCCA GGACCAATCA 2700
GTGAACCTG CTCGGAATTA AAGGCTTCCT CTGGGTGCCT GCTGAACAAC 2750
TGAGCTCATG TCATGGGCAT GTGGTGTTT CTCTGTTGCC TGAAGAGCC 2800
ATTAAGTCA GTCGTGCGTG AAGCATCTCT CTTCTAAAGG ATGTGTATTT 2850
CCATAAATGC TTTCTGAGGA TCCGGTACAA AATGATTTCC CAAAGTTCTG 2900
AAGTGCCTTG AGAACATGTG GGTCGAGTG TTATAACAGA CTCCTCCCCC 2950
GGGTCACCTT TTGCCTGGTC ATCCTGTTAG AGTACATCTT TGGAAATCCA 3000
GGGTAATATT CTCTTTCAGA GATGCTCATT GTGTAACCTCT GTGTAGGGAG 3050
ATAGTCACCT TAAACAGCTC AAAGTAGCTA GCTAAAGGAG TAGCCTTAAA 3100
TACCTAAAAG ATGACAGAAG CATAGCCCTT AACAAATCTT CAGCTTGCT 3150
CTCAGTATTT CCCAATCATG AAAATCCCTT GCTATGTCTT TCCTACTAGA 3200
AATGTTCTAG AATCGCTGA CGGTGGGTC AGAGGGCAGT CGGTATTTAG 3250
GCCGTGAGCT TCCCATACTA CTGCAGGTCC AACTCCTGGC AACCGCGGGC 3300
TCAAGGCAGG TCATTGGAAT CCACGTTTTG GCCACAGTAG TTGTAGGATT 3350
GCTTTTCTGT ATCATAATTT TAGAATGCTC TTAAATCTT GAGGAAGAGT 3400
TTTTATTTT TATTTATTT TGAGATGGAG TCTCTGTTGC CCAGGCTGCA 3450
GTGCAGTGGT GCCATCTCAG CTCACTGCAA CTCCACCTC CCAGGTTCAA 3500
GCGATTCTCC TGCTCAGCC ACCTGAGTAG CTGGGAGTAC AGGCATGTGG 3550
CACCATGCCCT GGCTAATTTT TGTATTTTTA ATAGAGTTGA GATTTCACCA 3600
TGATGTCAG GCTGGTCTCG AACTCCTGAC CTCGTGATCC GCCCGCCTCG 3650
GCCCCCAA GTGCTGGGAT TAACGGGTGT GAGCCACGGC GCCCAGCCCA 3700
GGAAGAGTTT TTAATTTAGA GCTCTGTTTA ATTATACCAC TGGGAAATCA 3750
TGGTTACGCT TCAGGCATAT TCTTCCCAG AGTACTACTT ACATTTTAAA 3800
TTTCATTTTG TAAAGTTAAA TGTCAGCATT CCCTTTAAA GTGTCCATTG 3850
TTCTTTGAAA GTAGACGTTT CAGTCATTCT TTTCAAACAA GTGTTTGTTG 3900

FIGURE 17A

ACCTTTTGCC AAGCTGTGGG CATCGTGTGT GAGTACAGGG TGCTCAGCTC 3950
TTCCACCGTC ATTTTGAATT GTTCACATGG GTAATTGGTC ATGGAAATGA 4000
TCAGATTGAC CTTGATTGAC TGTACAGGCAT GGCTTTGTTT CTAGTTTCAA 4050
TCTGTTCTCG TTCTTGTAC CGGATTATTC TACTCCTGCA ATGAACCCCTG 4100
TTGACACCGG ATTTAGCTCT TGTCGGCCTT CGTGGGGAGC TGTTTGTGTT 4150
AATATGAGCT ACTGCATGTA ATTCTTAAAC TGGGCTTGTC ACATTGTATT 4200
GTATTTTGTGATCTGTAAT GAAAAGAATC TGTA CTGCAA GTAAACCTA 4250
CTCCCCAAA ATGTGTGGCT TTGGGTCTGC ATTAACGCT GTAGTCCATG 4300
TTCATGCC 4308

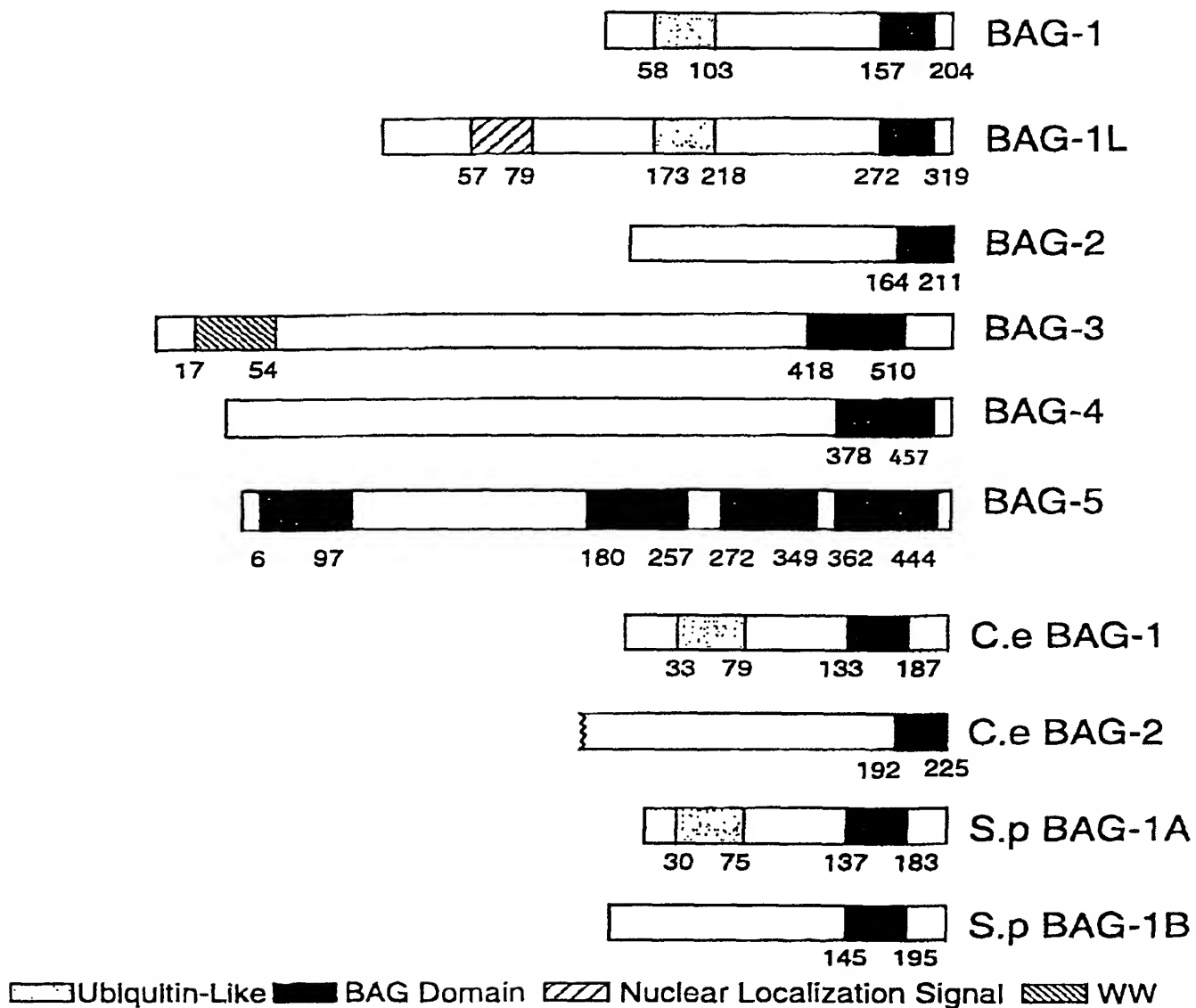
FIGURE 17B

MDMGNQHPSISRLQEIQKEV KSVEQQVIGF SGLSDDKNYK KLERILTKQL 50
FEIDSVDTGEG KGDQQARKR AAQETERLLK ELEQNANHPH RIEIQNIFEE 100
AQSLVREKIV PFYNGGNCVT DEFEEGIGQDI ILRLTHVKTG GKISLRKARY 150
HTLTKICAVQ EIIEDCMKKQ PSLPLSEDAH PSVAKINFVM CEVNKARGVL 200
IALLMGVNNN ETCRHLSCVL SGLIADLDAL DVCGRTEIRN YRREVVEDIN 250
KLLKYLDLEE EADTTKAFDL RQNHSLKIE KVLKRMREIK NELLQAQNP 300
ELYSSKTEL QGLIGQLDEV SLEKNPCIRE ARRRAVIEVQ TLITYIDLKE 350
ALEKRKL FAC EEHP SHKAVW NVLGNLSEIQ GEVLSFDG NR TDKNYIRLEE 400
LLTKQLLALD AVDPQGEEKC KAARKQAVRL AQNILSYLDL KSDEWEY 447

FIGURE 17C

CCCCCCCC CCCCCCCC CCGGAGAGCG CCGGAGCGCG CTCTGCGACC CAGTGGCGCC CCGTTCACCC CTTCCCCCCC TCGAGCTBGC 90
 TCGGAGCGCG TCGGAGCGCAT CGAGCTGCGG CCGGAGCTCC CTTCCCGGAC CCGGTHAGCG CCGTATCTTC CAGCTGCGCA CCGGAGCGAC 180
 CCGGAGCGCA CAGCGCATCC CAGTCACTCT TCTTTGCTTC CTCTGGAAC TCGAGCAGAC AAGAGCTTGC ATHTGCGAMA CCGAGATCCT 270
 M B M C H Q E ?
 TCTTTGCTH CCGTTCACCA ATTCGAAAC CAGTTHAGAA CTCTGGAACA CCGAGTHTC CCGTTCACCT CTTCTGCAAC TCGAGCAAT 340
 S I S V L Q I I Q K I V K S V I Q Q V I G I S G L S B B K H
 TCGAGCAAC TCGAGCAAT TCTHAGAAA CAGCTTTTC CAGTCACTC TCTGAGTCT CAGGCAAAAC CAGATHTTC CAGAGCTTGC 450
 Y K K L I R I L T K Q L F I I B S V B T I G K G B I Q Q A R
 AAGCGCGAC CAGAGGAGAC AGAGCTCTT CTGAGCACT TCGAGCGAA TCGAGCAAC CAGAGCGCA TCTHAGTTC CAGAGCTTTC 540
 K R A A Q I T I R L L K E L I Q M A H E P E R I I I Q M I I
 CAGGAGCGC AGCTCTCTT CAGAGAGAA ATTCGCAAT TCTHAGTTC AGGAGCTC CAGAGCTC AGTTCGAA AGGAGCTC 630
 I I A Q S L V R I K I V P I Y H G G H C V T B I I I I G I Q
 CAGTCACTC TCGAGCTC ACATCTTAA ACTGAGGAA AATCTCTT CCGGAGCA CAGTTCACA CTTTACCA AATCTCTC 720
 B I I L R L I K T G K I S L R K A R Y E T L T K I C A
 CTGAGCAAC TCTGAGAA CTGAGTAA AAGAGCTT CCGTCTCTT TCGAGCAAT CAGAGCTT CCGTCTCTT AATCACTT 810
 V Q I I I I B C H K K Q P S L P L S I B A K P S V A K I H I
 CTGAGCTC AGTTCAGAA CCGCGGCG CCGTCTCTT CAGTTCAT CCGTCTCTT AAGAGCTC CCGTCTCTT CTTTCTCTT 900
 V H C I V H K A A G V L I A L L M G V H M H I T C R E L S C
 CCGTCTCTT CCGTCTCTT TCGAGCAAT CCGTCTCTT TCGAGCAAT CCGAGCTC CAGAGCTC AAGAGCTC CAGAGCTC 990
 V L S G L I A B L B A L B V C G R T E I R H I R R E V V E B
 ATCAAGCAAT TCTGAGTTC CAGAGCAAC CAGAGCAAC CAGAGCTT CAGAGCTC AAGAGCTC CAGAGCTC CAGAGCTC 1080
 I H K L I H I I L I I A B T T K A I B L R Q M H S I L K
 ATCAAGCAAC TCTGAGCAAT ATCAAGCAAT AATCTCTT AAGAGCTC CCGTCTCTT TCTGAGTTC CCGAGCAAC 1170
 I E K V L K R M A I I K H I L L Q A Q M P S I L Y L S S K T
 CAGTCTCTT CTTTCTCTT CAGAGCTC CAGAGCTC TCGAGCAAC CCGTCTCTT CCGAGCAAC CAGAGCTC CAGAGCTC 1260
 I L Q G L I G I V S L I K M P C I R E A R R A V I I
 CTGAGCTC TCTGAGTTC TCTGAGTTC AAGAGCTC TCGAGCAAC AAGAGCTT CCGTCTCTT CCGAGCTC CAGAGCTC 1350
 V Q T L I T I I B L K I A L I K R K L I A C I E E E P S E K A
 CTGAGCTC TCTGAGTTC TCTGAGTTC AAGAGCTC AAGAGCTT AATCTCTT AATCTCTT AATCTCTT AATCTCTT 1440
 V H N V L E M I S I I G I V L S I B G M R T B K H Y I R L
 CAGAGCTC TCGAGCAAC CCGTCTCTT CCGTCTCTT TCGAGCAAC CCGAGCAAC AAGAGCTC CCGAGCAAC AAGAGCTC 1530
 I I L L T K Q L L A L B A V B P Q G Y I K C K A A R K Q A V
 AAGAGCTC AAGAGCTT CAGAGCTC CAGAGCTC CAGAGCTC CAGAGCTC CAGAGCTC CAGAGCTC CAGAGCTC 1620
 R L A Q M I L S Y L B L K S B E W X Y .
 TCGAGCTC TCTGAGTTC TCTGAGTTC CAGAGCTC TCGAGCTC TCTGAGTTC TCTGAGTTC TCGAGCTC TCGAGCTC 1710
 AATCTCTT CAGAGCTC TCTGAGTTC CAGAGCTC AATCTCTT AAGAGCTC AATCTCTT TCGAGCTC TCTGAGTTC 1800
 ATCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC 1890
 CCGAGCTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC 1980
 TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC 2070
 CAGAGCTC CAGAGCTC CAGAGCTC CAGAGCTC CAGAGCTC CAGAGCTC CAGAGCTC CAGAGCTC 2160
 ATCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC 2250
 CAGAGCTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC 2340
 TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC 2430
 TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC 2520
 CAGAGCTC CAGAGCTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC 2610
 CAGAGCTC CAGAGCTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC 2700
 CAGAGCTC CAGAGCTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC 2790
 TCGAGCTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC 2880
 AATCTCTT CAGAGCTC AATCTCTT AATCTCTT AATCTCTT AATCTCTT AATCTCTT AATCTCTT AATCTCTT 2970
 ATCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC 3060
 TCGAGCTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC 3150
 CAGAGCTC CAGAGCTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC 3240
 CAGAGCTC CAGAGCTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC 3330
 CAGAGCTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC 3420
 TCGAGCTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC 3510
 TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC 3600
 CAGAGCTC CAGAGCTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC 3690
 CAGAGCTC CAGAGCTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC 3780
 AATCTCTT AATCTCTT TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC 3870
 CAGAGCTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC 3960
 ATCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC 4050
 TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC 4140
 ATCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC 4230
 TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC TCTGAGTTC 4320

FIGURE 18



SEQUENCE LISTING

<110> Reed, John C.
Takayama, Shinichi
The Burnham Institute

<120> Novel BAG Proteins and Nucleic Acid Molecules Encoding Them

<130> FP-LJ 3646

<140>
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Ser	Glu	Glu	Ala	Thr	Gln	Ser	Glu	Glu	Ala	Thr	Gln	Gly	Glu	Glu	Met	
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Thr Arg Ser Glu Glu Leu Thr Arg Ser Glu Glu Leu Thr Leu Ser Glu
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Phe Pro Ser Gly Ser Glu Glu Ala Ile Ser Arg His Phe His Pro Ser
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Gly	Glu	Ala	Glu	Ala	Pro	Pro	Lys	His	Pro	Gly	Val	Leu	Lys	Val	Glu	
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245	250	255
Ala Ala Ala Ala Ala Ala Gln Pro Pro Ala Ser His Gly Pro Glu Arg		
260	265	270
Ser Gln Ser Pro Ala Ala Ser Asp Cys Ser Ser Ser Ser Ser Ser Ala		
275	280	285
Ser Leu Pro Ser Ser Gly Arg Ser Ser Leu Gly Ser His Gln Leu Pro		
290	295	300
Arg Gly Tyr Ile Ser Ile Pro Val Ile His Glu Gln Asn Val Thr Arg		
305	310	315
Pro Ala Ala Gln Pro Ser Phe His Lys Ala Gln Lys Thr His Tyr Pro		
325	330	335
Ala Gln Arg Gly Glu Tyr Gln Thr His Gln Pro Val Tyr His Lys Ile		
340	345	350
Gln Gly Asp Asp Trp Glu Pro Arg Pro Leu Arg Ala Ala Ser Pro Phe		
355	360	365
Arg Ser Ser Val Gln Gly Ala Ser Ser Arg Glu Gly Ser Pro Ala Arg		
370	375	380
Ser Ser Thr Pro Leu His Ser Pro Ser Pro Ile Arg Val His Thr Val		
385	390	395
Val Asp Arg Pro Gln Gln Pro Met Thr His Arg Glu Thr Ala Pro Val		
405	410	415
Ser Gln Pro Glu Asn Lys Pro Glu Ser Lys Pro Gly Pro Val Gly Pro		
420	425	430
Glu Leu Pro Pro Gly His Ile Pro Ile Gln Val Ile Arg Lys Glu Val		

435		440		445
Asp Ser Lys Pro Val Ser Gln Lys Pro Pro Pro Pro Ser Glu Lys Val				
450		455		460
Glu Val Lys Val Pro Pro Ala Pro Val Pro Cys Pro Pro Pro Ser Pro				
465		470		475
				480
Gly Pro Ser Ala Val Pro Ser Ser Pro Lys Ser Val Ala Thr Glu Glu				
	485		490	495
Arg Ala Ala Pro Ser Thr Ala Pro Ala Glu Ala Thr Pro Pro Lys Pro				
	500		505	510
Gly Glu Ala Glu Ala Pro Pro Lys His Pro Gly Val Leu Lys Val Glu				
	515		520	525
Ala Ile Leu Glu Lys Val Gln Gly Leu Glu Gln Ala Val Asp Asn Phe				
	530		535	540
Glu Gly Lys Lys Thr Asp Lys Lys Tyr Leu Met Ile Glu Glu Tyr Leu				
	545		550	555
				560
Thr Lys Glu Leu Leu Ala Leu Asp Ser Val Asp Pro Glu Gly Arg Ala				
	565		570	575
Asp Val Arg Gln Ala Arg Arg Asp Gly Val Arg Lys Val Gln Thr Ile				
	580		585	590
Leu Glu Lys Leu Glu Gln Lys Ala Ile Asp Val Pro Gly Gln Val Gln				
	595		600	605
Val Tyr Glu Leu Gln Pro Ser Asn Leu Glu Ala Asp Gln Pro Leu Gln				
	610		615	620
Ala Ile Met Glu Met Gly Ala Val Ala Ala Asp Lys Gly Lys Lys Asn				
	625		630	635
				640
Ala Gly Asn Ala Glu Asp Pro His Thr Glu Thr Gln Gln Pro Glu Ala				
	645		650	655
Thr Ala Ala Ala Thr Ser Asn Pro Ser Ser Met Thr Asp Thr Pro Gly				
	660		665	670
Asn Pro Ala Ala Pro				
	675			

<210> 7

 $\langle 211 \rangle$ 1010

<212> DNA

<213> Homo sapiens

 $\langle 220 \rangle$

<221> CDS

 $\langle 222 \rangle \quad (323) \dots (1009)$

<400> 7

acgatatcct gtaagaccaa gaattgcaag gccagagttt gaattcttat acaaatggag	60
cgtatggtcc aacatacccc ccaggccctg gggcaaatac tgcctcatac tcagggggctt	120
attatgcacc tggttatact cagaccagtt actccacaga agttccaagt acttaccgtt	180
catctggcaa cagcccaact ccagtctctc gttggatcta tccccagcag gactgtcaag	240
actgaagcac cccctcttaa ggggcagggt ccaggatata cgccttcaca gaaccctgga	300
atgaccctgc cccattatcc tt atg gag atg gta atc gta gtg ttc cac aat	352
Met Glu Met Val Ile Val Val Phe His Asn	
1 5 10	
cac ggc cga ctg tac gac cac aag aaa gat gcg tgg gct tct cct ggt	400
His Gly Arg Leu Tyr Asp His Lys Lys Asp Ala Trp Ala Ser Pro Gly	
15 20 25	
gct tat gga atg ggt ggc cgt tat ccc tgg cct tca tca gcg ccc tca	448
Ala Tyr Gly Met Gly Gly Arg Tyr Pro Trp Pro Ser Ser Ala Pro Ser	
30 35 40	
gca cca ccc ggc aat ctc tac atg act gaa agt act tca cca tgg cct	496
Ala Pro Pro Gly Asn Leu Tyr Met Thr Glu Ser Thr Ser Pro Trp Pro	
45 50 55	
agc agt ggc tct ccc cag tca ccc cct tca ccc cca gtc cag cag ccc	544
Ser Ser Gly Ser Pro Gln Ser Pro Pro Ser Pro Pro Val Gln Gln Pro	
60 65 70	
aag gat tct tca tac ccc tat agc caa tca gat caa agc atg aac cgg	592
Lys Asp Ser Ser Tyr Pro Tyr Ser Gln Ser Asp Gln Ser Met Asn Arg	
75 80 85 90	
cac aac ttt cct tgc agt gtc cat cag tac gaa tcc tcg ggg aca gtg	640
His Asn Phe Pro Cys Ser Val His Gln Tyr Glu Ser Ser Gly Thr Val	
95 100 105	

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aac aat gat gat tca gat ctt ttg gat tcc caa gtc cag tat agt gct      688
Asn Asn Asp Asp Ser Asp Leu Leu Asp Ser Gln Val Gln Tyr Ser Ala
      110                      115                      120

gag cct cag ctg tat ggt aat gcc acc agt gac cat ccc aac aat caa      736
Glu Pro Gln Leu Tyr Gly Asn Ala Thr Ser Asp His Pro Asn Asn Gln
      125                      130                      135

gat caa agt agc agt ctt cct gaa gaa tgt gta cct tca gat gaa agt      784
Asp Gln Ser Ser Ser Leu Pro Glu Glu Cys Val Pro Ser Asp Glu Ser
      140                      145                      150

act cct ccg agt att aaa aaa atc ata cat gtg ctg gag aag gtc cag      832
Thr Pro Pro Ser Ile Lys Lys Ile Ile His Val Leu Glu Lys Val Gln
      155                      160                      165                      170

tat ctt gaa caa gaa gta gaa gaa ttt gta gga aaa aag aca gac aaa      880
Tyr Leu Glu Gln Glu Val Glu Glu Phe Val Gly Lys Lys Thr Asp Lys
      175                      180                      185

gca tac tgg ctt ctg gaa gaa atg cta acc aag gaa ctt ttg gaa ctg      928
Ala Tyr Trp Leu Leu Glu Glu Met Leu Thr Lys Glu Leu Leu Glu Leu
      190                      195                      200

gat tca gtt gaa act ggg ggc cag gac tct gta cgg cag gcc aga aaa      976
Asp Ser Val Glu Thr Gly Gly Gln Asp Ser Val Arg Gln Ala Arg Lys
      205                      210                      215

gag gct gtt tgt aag att cag gcc ata ttg gaa a                        1010
Glu Ala Val Cys Lys Ile Gln Ala Ile Leu Glu
      220                      225

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<210> 8

<211> 229

<212> PRT

<213> Homo sapiens

<400> 8

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Met Glu Met Val Ile Val Val Phe His Asn His Gly Arg Leu Tyr Asp
  1                      5                      10                      15

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His Lys Lys Asp Ala Trp Ala Ser Pro Gly Ala Tyr Gly Met Gly Gly
      20                      25                      30

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Arg Tyr Pro Trp Pro Ser Ser Ala Pro Ser Ala Pro Pro Gly Asn Leu
      35                      40                      45

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Tyr Met Thr Glu Ser Thr Ser Pro Trp Pro Ser Ser Gly Ser Pro Gln
 50 55 60
 Ser Pro Pro Ser Pro Pro Val Gln Gln Pro Lys Asp Ser Ser Tyr Pro
 65 70 75 80
 Tyr Ser Gln Ser Asp Gln Ser Met Asn Arg His Asn Phe Pro Cys Ser
 85 90 95
 Val His Gln Tyr Glu Ser Ser Gly Thr Val Asn Asn Asp Asp Ser Asp
 100 105 110
 Leu Leu Asp Ser Gln Val Gln Tyr Ser Ala Glu Pro Gln Leu Tyr Gly
 115 120 125
 Asn Ala Thr Ser Asp His Pro Asn Asn Gln Asp Gln Ser Ser Ser Leu
 130 135 140
 Pro Glu Glu Cys Val Pro Ser Asp Glu Ser Thr Pro Pro Ser Ile Lys
 145 150 155 160
 Lys Ile Ile His Val Leu Glu Lys Val Gln Tyr Leu Glu Gln Glu Val
 165 170 175
 Glu Glu Phe Val Gly Lys Lys Thr Asp Lys Ala Tyr Trp Leu Leu Glu
 180 185 190
 Glu Met Leu Thr Lys Glu Leu Leu Glu Leu Asp Ser Val Glu Thr Gly
 195 200 205
 Gly Gln Asp Ser Val Arg Gln Ala Arg Lys Glu Ala Val Cys Lys Ile
 210 215 220
 Gln Ala Ile Leu Glu
 225

<210> 9

<211> 689

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (3)..(482)

<220>

<221> unsure

<222> (105)

<223> any amino acid

<400> 9

ga gaa ata aaa aat gaa ctt ctc caa gca caa aac cct tct gaa ttg 47
 Glu Ile Lys Asn Glu Leu Leu Gln Ala Gln Asn Pro Ser Glu Leu
 1 5 10 15

tac ctg agc tcc aaa aca gaa ttg cag ggt tta att gga cag ttg gat 95
 Tyr Leu Ser Ser Lys Thr Glu Leu Gln Gly Leu Ile Gly Gln Leu Asp
 20 25 30

gag gta agt ntt gaa aaa aac ccc tgc atc cgg gaa gcc agg aga aga 143
 Glu Val Ser Xaa Glu Lys Asn Pro Cys Ile Arg Glu Ala Arg Arg Arg
 35 40 45

gca gtg atc gag gtg caa act ctg atc aca tat att gac ttg aag gag 191
 Ala Val Ile Glu Val Gln Thr Leu Ile Thr Tyr Ile Asp Leu Lys Glu
 50 55 60

gcc ctt gag aaa aga aag ctg ttt gct tgt gag gag cac cca tcc cat 239
 Ala Leu Glu Lys Arg Lys Leu Phe Ala Cys Glu Glu His Pro Ser His
 65 70 75

aaa gcc gtc tgg aac gtc ctt gga aac ttg tct gag atc cag gga gaa 287
 Lys Ala Val Trp Asn Val Leu Gly Asn Leu Ser Glu Ile Gln Gly Glu
 80 85 90 95

gtt ctt tca ttt gat gga aat cga acc gat aag aac tac atc cgg ctg 335
 Val Leu Ser Phe Asp Gly Asn Arg Thr Asp Lys Asn Tyr Ile Arg Leu
 100 105 110

gaa gag ctg ctc acc aag cag ctg cta gcc ctg gat gct gtt gat ccg 383
 Glu Glu Leu Leu Thr Lys Gln Leu Leu Ala Leu Asp Ala Val Asp Pro
 115 120 125

cag gga gaa gag aag tgt aag gct gcc agg aaa caa gct gtg agg ctt 431
 Gln Gly Glu Glu Lys Cys Lys Ala Ala Arg Lys Gln Ala Val Arg Leu
 130 135 140

gcg cag aat att ctc agc tat ctc gac ctg aaa tct gat gaa tgg gag 479
 Ala Gln Asn Ile Leu Ser Tyr Leu Asp Leu Lys Ser Asp Glu Trp Glu
 145 150 155

tac tgaaatacca gagatctcac ttttgataact gttttgcact tcatatgtgc 532
 Tyr
 160

ttctatgtat agagagcttt cagttcattg atttatacgt gcatatttca gtctcagtat 592
 ttatgattga agcaaattct attcagtatc tgctgctttt gatgttgcaa gacaaatatac 652
 attacagcac gttaactttt ccattcggat caaaaaa 689

<210> 10

<211> 160

<212> PRT

<213> Homo sapiens

<400> 10

Glu Ile Lys Asn Glu Leu Leu Gln Ala Gln Asn Pro Ser Glu Leu Tyr
 1 5 10 15

Leu Ser Ser Lys Thr Glu Leu Gln Gly Leu Ile Gly Gln Leu Asp Glu
 20 25 30

Val Ser Xaa Glu Lys Asn Pro Cys Ile Arg Glu Ala Arg Arg Arg Ala
 35 40 45

Val Ile Glu Val Gln Thr Leu Ile Thr Tyr Ile Asp Leu Lys Glu Ala
 50 55 60

Leu Glu Lys Arg Lys Leu Phe Ala Cys Glu Glu His Pro Ser His Lys
 65 70 75 80

Ala Val Trp Asn Val Leu Gly Asn Leu Ser Glu Ile Gln Gly Glu Val
 85 90 95

Leu Ser Phe Asp Gly Asn Arg Thr Asp Lys Asn Tyr Ile Arg Leu Glu
 100 105 110

Glu Leu Leu Thr Lys Gln Leu Leu Ala Leu Asp Ala Val Asp Pro Gln
 115 120 125

Gly Glu Glu Lys Cys Lys Ala Ala Arg Lys Gln Ala Val Arg Leu Ala
 130 135 140

Gln Asn Ile Leu Ser Tyr Leu Asp Leu Lys Ser Asp Glu Trp Glu Tyr
 145 150 155 160

<210> 11

<211> 246

<212> DNA

<213> Caenorhabditis elegans

<400> 11

atgtctttcc gcctcttcgt tgaaatattt cactttcttt tccagctttt tccccatctc 60
 gacctgcttt ggtttttcga gaaaaccacg ttccaaatca gcgacatctc tcaaattgag 120
 atcataggct ttttgaagat tgctcaaatt atgctttctca tattgcatga gcattttgaa 180
 gccgcggtca tcaaccaaag cattttttcc acccatcaca atgattttat cattttcttt 240
 aaaatt 246

<210> 12

<211> 210

<212> PRT

<213> Caenorhabditis elegans

<400> 12

Met Lys Val Asn Val Ser Cys Ser Ser Val Gln Thr Thr Ile Asp Ile
 1 5 10 15
 Leu Glu Glu Asn Gln Gly Glu Asp Glu Ser Ile Leu Thr Leu Gly Gln
 20 25 30
 Leu Arg Asp Arg Ile Ala Thr Asp Asn Asp Val Asp Val Glu Thr Met
 35 40 45
 Lys Leu Leu His Arg Gly Lys Phe Leu Gln Gly Ala Asp Asp Val Ser
 50 55 60
 Leu Ser Thr Leu Asn Phe Lys Glu Asn Asp Lys Ile Ile Val Met Gly
 65 70 75 80
 Gly Lys Asn Ala Leu Val Asp Asp Ala Gly Phe Lys Met Leu Met Gln
 85 90 95
 Tyr Glu Lys His Asn Leu Ser Asn Leu Gln Lys Ala Tyr Asp Leu Asn
 100 105 110
 Leu Arg Asp Val Ala Asp Leu Glu Arg Gly Phe Leu Glu Lys Pro Lys
 115 120 125
 Gln Val Glu Met Gly Lys Lys Leu Glu Lys Lys Val Lys Tyr Phe Asn
 130 135 140
 Glu Glu Ala Glu Arg His Leu Glu Thr Leu Asp Gly Met Asn Ile Ile
 145 150 155 160

Thr Glu Thr Thr Pro Glu Asn Gln Ala Lys Arg Asn Arg Glu Lys Arg
 165 170 175

Lys Thr Leu Val Asn Gly Ile Gln Thr Leu Leu Asn Gln Asn Asp Ala
 180 185 190

Leu Leu Arg Arg Leu Gln Glu Tyr Gln Ser Val Leu Asn Gly Asp Ile
 195 200 205

Pro Glu
 210

<210> 13

<211> 1377

<212> DNA

<213> *Caenorhabditis elegans*

<220>

<221> CDS

<222> (1)..(1377)

<400> 13

atg cca gtc gtg aac ata cca atc aaa ata ctt ggt cag aat caa tca 48
 Met Pro Val Val Asn Ile Pro Ile Lys Ile Leu Gly Gln Asn Gln Ser
 1 5 10 15

cat agt cga agt aac tcc tcg tct tct gtt gac aac gat cga aat caa 96
 His Ser Arg Ser Asn Ser Ser Ser Ser Val Asp Asn Asp Arg Asn Gln
 20 25 30

cca cca cag cag cca cct caa ccg caa cca caa cag caa tct cag caa 144
 Pro Pro Gln Gln Pro Pro Gln Pro Gln Pro Gln Gln Gln Ser Gln Gln
 35 40 45

caa tac cag cag gct cca aac gtg aat acc aat atg cat cat tcc aac 192
 Gln Tyr Gln Gln Ala Pro Asn Val Asn Thr Asn Met His His Ser Asn
 50 55 60

gga ttc tca cct aac ttc cca tct cgt agt cct att ccg gac ttt ccc 240
 Gly Phe Ser Pro Asn Phe Pro Ser Arg Ser Pro Ile Pro Asp Phe Pro
 65 70 75 80

agt ttt tca tct ggg ttc cca aac gat tct gaa tgg tct tcg aat ttc 288
 Ser Phe Ser Ser Gly Phe Pro Asn Asp Ser Glu Trp Ser Ser Asn Phe
 85 90 95

ccg tcg ttt cca aat ttc cca agt gga ttc tca aat gga agt tct aat	336
Pro Ser Phe Pro Asn Phe Pro Ser Gly Phe Ser Asn Gly Ser Ser Asn	
100 105 110	
ttc cct gat ttt cca aga ttc gga aga gat gga gga cta tcg cca aac	384
Phe Pro Asp Phe Pro Arg Phe Gly Arg Asp Gly Gly Leu Ser Pro Asn	
115 120 125	
cca ccg atg caa gga tac agg aga agt cca aca cca aca tca act caa	432
Pro Pro Met Gln Gly Tyr Arg Arg Ser Pro Thr Pro Thr Ser Thr Gln	
130 135 140	
tct cca act tct aca tta aga cgc aac tct cag cag aat caa gct cct	480
Ser Pro Thr Ser Thr Leu Arg Arg Asn Ser Gln Gln Asn Gln Ala Pro	
145 150 155 160	
cca caa tat tct cag caa caa cca caa caa gct caa caa cgt cag aca	528
Pro Gln Tyr Ser Gln Gln Gln Pro Gln Gln Ala Gln Gln Arg Gln Thr	
165 170 175	
act cct ccg tca aca aaa gct tca tct cga cca cca tct cgt act cgt	576
Thr Pro Pro Ser Thr Lys Ala Ser Ser Arg Pro Pro Ser Arg Thr Arg	
180 185 190	
gaa cca aag gaa cct gag gta ccc gag aga cca gca gtt att cca ttg	624
Glu Pro Lys Glu Pro Glu Val Pro Glu Arg Pro Ala Val Ile Pro Leu	
195 200 205	
cca tat gag aag aag gag aaa cca ctg gag aag aaa ggt agt cgt gat	672
Pro Tyr Glu Lys Lys Glu Lys Pro Leu Glu Lys Lys Gly Ser Arg Asp	
210 215 220	
tct gga aag ggt gat gag aac ctt gaa gag aac att gcc aag atc acg	720
Ser Gly Lys Gly Asp Glu Asn Leu Glu Glu Asn Ile Ala Lys Ile Thr	
225 230 235 240	
atc gga aag aat aat tgc gag tta tgt ccg gaa caa gaa acg gac ggc	768
Ile Gly Lys Asn Asn Cys Glu Leu Cys Pro Glu Gln Glu Thr Asp Gly	
245 250 255	
gac cca tct cca cta acc tcc cca atc acc gaa gga aag cca aag aga	816
Asp Pro Ser Pro Leu Thr Ser Pro Ile Thr Glu Gly Lys Pro Lys Arg	
260 265 270	
gga aag aaa ctt caa cgt aat caa agt gtt gtt gat ttc aat gcc aag	864
Gly Lys Lys Leu Gln Arg Asn Gln Ser Val Val Asp Phe Asn Ala Lys	
275 280 285	

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aca att gtt act ttg gat aaa att gaa tta caa gtt gag cag ttg aga 912
Thr Ile Val Thr Leu Asp Lys Ile Glu Leu Gln Val Glu Gln Leu Arg
      290                      295                      300

aaa aaa gct gct gaa ctc gaa atg gaa aaa gag caa att ctt cgt tct 960
Lys Lys Ala Ala Glu Leu Glu Met Glu Lys Glu Gln Ile Leu Arg Ser
305                      310                      315                      320

cta gga gaa atc agt gtt cat aac tgc atg ttc aaa ctg gaa gaa tgt 1008
Leu Gly Glu Ile Ser Val His Asn Cys Met Phe Lys Leu Glu Glu Cys
                      325                      330                      335

gat cgt gaa gag att gaa gca atc act gac cga ttg aca aaa aga aca 1056
Asp Arg Glu Glu Ile Glu Ala Ile Thr Asp Arg Leu Thr Lys Arg Thr
                      340                      345                      350

aag aca gtt caa gtt gtt gtc gaa act cca cga aat gaa gaa cag aaa 1104
Lys Thr Val Gln Val Val Val Glu Thr Pro Arg Asn Glu Glu Gln Lys
      355                      360                      365

aaa gca ctg gaa gat gca act ttg atg atc gat gaa gtc gga gaa atg 1152
Lys Ala Leu Glu Asp Ala Thr Leu Met Ile Asp Glu Val Gly Glu Met
      370                      375                      380

atg cat tcg aat att gaa aag gct aag ctg tgc cta caa acc tac atg 1200
Met His Ser Asn Ile Glu Lys Ala Lys Leu Cys Leu Gln Thr Tyr Met
385                      390                      395                      400

aac gcc tgt tcg tac gaa gaa act gct gga gcc acc tgc caa aac ttc 1248
Asn Ala Cys Ser Tyr Glu Glu Thr Ala Gly Ala Thr Cys Gln Asn Phe
                      405                      410                      415

ttg aag atc ata att cag tgc gct gct gat gat cag aaa cgc atc aag 1296
Leu Lys Ile Ile Ile Gln Cys Ala Ala Asp Asp Gln Lys Arg Ile Lys
      420                      425                      430

cgt cgt ctg gaa aat ctg atg tct caa att gag aat gct gag aga acg 1344
Arg Arg Leu Glu Asn Leu Met Ser Gln Ile Glu Asn Ala Glu Arg Thr
      435                      440                      445

aaa gca gat ttg atg gat gat caa agc gaa tag 1377
Lys Ala Asp Leu Met Asp Asp Gln Ser Glu
      450                      455

<210> 14
<211> 458
<212> PRT

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<213> Caenorhabditis elegans

<400> 14

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Met Pro Val Val Asn Ile Pro Ile Lys Ile Leu Gly Gln Asn Gln Ser
 1              5              10              15

His Ser Arg Ser Asn Ser Ser Ser Ser Val Asp Asn Asp Arg Asn Gln
          20              25              30

Pro Pro Gln Gln Pro Pro Gln Pro Gln Pro Gln Gln Gln Ser Gln Gln
          35              40              45

Gln Tyr Gln Gln Ala Pro Asn Val Asn Thr Asn Met His His Ser Asn
 50              55              60

Gly Phe Ser Pro Asn Phe Pro Ser Arg Ser Pro Ile Pro Asp Phe Pro
65              70              75              80

Ser Phe Ser Ser Gly Phe Pro Asn Asp Ser Glu Trp Ser Ser Asn Phe
          85              90              95

Pro Ser Phe Pro Asn Phe Pro Ser Gly Phe Ser Asn Gly Ser Ser Asn
          100              105              110

Phe Pro Asp Phe Pro Arg Phe Gly Arg Asp Gly Gly Leu Ser Pro Asn
          115              120              125

Pro Pro Met Gln Gly Tyr Arg Arg Ser Pro Thr Pro Thr Ser Thr Gln
          130              135              140

Ser Pro Thr Ser Thr Leu Arg Arg Asn Ser Gln Gln Asn Gln Ala Pro
          145              150              155              160

Pro Gln Tyr Ser Gln Gln Gln Pro Gln Gln Ala Gln Gln Arg Gln Thr
          165              170              175

Thr Pro Pro Ser Thr Lys Ala Ser Ser Arg Pro Pro Ser Arg Thr Arg
          180              185              190

Glu Pro Lys Glu Pro Glu Val Pro Glu Arg Pro Ala Val Ile Pro Leu
          195              200              205

Pro Tyr Glu Lys Lys Glu Lys Pro Leu Glu Lys Lys Gly Ser Arg Asp
          210              215              220

Ser Gly Lys Gly Asp Glu Asn Leu Glu Glu Asn Ile Ala Lys Ile Thr
          225              230              235              240

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Ile Gly Lys Asn Asn Cys Glu Leu Cys Pro Glu Gln Glu Thr Asp Gly
      245                      250                      255

Asp Pro Ser Pro Leu Thr Ser Pro Ile Thr Glu Gly Lys Pro Lys Arg
      260                      265                      270

Gly Lys Lys Leu Gln Arg Asn Gln Ser Val Val Asp Phe Asn Ala Lys
      275                      280                      285

Thr Ile Val Thr Leu Asp Lys Ile Glu Leu Gln Val Glu Gln Leu Arg
      290                      295                      300

Lys Lys Ala Ala Glu Leu Glu Met Glu Lys Glu Gln Ile Leu Arg Ser
305                      310                      315                      320

Leu Gly Glu Ile Ser Val His Asn Cys Met Phe Lys Leu Glu Glu Cys
      325                      330                      335

Asp Arg Glu Glu Ile Glu Ala Ile Thr Asp Arg Leu Thr Lys Arg Thr
      340                      345                      350

Lys Thr Val Gln Val Val Val Glu Thr Pro Arg Asn Glu Glu Gln Lys
      355                      360                      365

Lys Ala Leu Glu Asp Ala Thr Leu Met Ile Asp Glu Val Gly Glu Met
      370                      375                      380

Met His Ser Asn Ile Glu Lys Ala Lys Leu Cys Leu Gln Thr Tyr Met
385                      390                      395                      400

Asn Ala Cys Ser Tyr Glu Glu Thr Ala Gly Ala Thr Cys Gln Asn Phe
      405                      410                      415

Leu Lys Ile Ile Ile Gln Cys Ala Ala Asp Asp Gln Lys Arg Ile Lys
      420                      425                      430

Arg Arg Leu Glu Asn Leu Met Ser Gln Ile Glu Asn Ala Glu Arg Thr
      435                      440                      445

Lys Ala Asp Leu Met Asp Asp Gln Ser Glu
      450                      455

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<210> 15

<211> 588

<212> DNA

<213> Schizosaccharomyces pombe

<220>

<221> CDS

<222> (1)..(588)

<400> 15

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atg tca gaa aag act agc aca gtt aca ata cac tat gga aat cag cga      48
Met Ser Glu Lys Thr Ser Thr Val Thr Ile His Tyr Gly Asn Gln Arg
   1             5             10             15

ttt ccg gta gca gtc aat cta aat gag acg tta agt gaa ctg att gat      96
Phe Pro Val Ala Val Asn Leu Asn Glu Thr Leu Ser Glu Leu Ile Asp
           20           25           30

gat tta ctt gaa acg act gag att tct gag aag aaa gtc aag ctt ttt     144
Asp Leu Leu Glu Thr Thr Glu Ile Ser Glu Lys Lys Val Lys Leu Phe
           35           40           45

tac gct ggc aag cgt tta aaa gac aaa aaa gcc tcg tta tca aaa ttg     192
Tyr Ala Gly Lys Arg Leu Lys Asp Lys Lys Ala Ser Leu Ser Lys Leu
           50           55           60

ggt tta aaa aat cat agt aaa att cta tgt ata aga cca cat aag caa     240
Gly Leu Lys Asn His Ser Lys Ile Leu Cys Ile Arg Pro His Lys Gln
           65           70           75           80

caa cga ggt tcc aag gaa aaa gac acg gtt gag ccc gct ccg aaa gcg     288
Gln Arg Gly Ser Lys Glu Lys Asp Thr Val Glu Pro Ala Pro Lys Ala
           85           90           95

gaa gcg gag aat cct gta ttt tcg cgt att tct gga gaa ata aaa gcc     336
Glu Ala Glu Asn Pro Val Phe Ser Arg Ile Ser Gly Glu Ile Lys Ala
           100          105          110

atc gat cag tat gtt gac aaa gaa ctt tcc ccc atg tac gac aat tac     384
Ile Asp Gln Tyr Val Asp Lys Glu Leu Ser Pro Met Tyr Asp Asn Tyr
           115          120          125

gta aat aaa ccg tcg aac gat cca aag cag aaa aac aaa cag aaa cta     432
Val Asn Lys Pro Ser Asn Asp Pro Lys Gln Lys Asn Lys Gln Lys Leu
           130          135          140

atg ata agt gaa cta ctt tta caa cag ctt tta aaa ttg gat gga gtt     480
Met Ile Ser Glu Leu Leu Leu Gln Gln Leu Leu Lys Leu Asp Gly Val
          145           150           155           160

gac gta ctg ggc agc gag aaa ttg cgt ttt gaa cgg aag caa ctt gtt     528
Asp Val Leu Gly Ser Glu Lys Leu Arg Phe Glu Arg Lys Gln Leu Val
           165          170           175

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tct aag atc caa aaa atg ttg gat cac gtt gac caa aca agc caa gaa 576
 Ser Lys Ile Gln Lys Met Leu Asp His Val Asp Gln Thr Ser Gln Glu
 180 185 190

gtg gcc gca tag 588
 Val Ala Ala
 195

<210> 16

<211> 195

<212> PRT

<213> Schizosaccharomyces pombe

<400> 16

Met Ser Glu Lys Thr Ser Thr Val Thr Ile His Tyr Gly Asn Gln Arg
 1 5 10 15

Phe Pro Val Ala Val Asn Leu Asn Glu Thr Leu Ser Glu Leu Ile Asp
 20 25 30

Asp Leu Leu Glu Thr Thr Glu Ile Ser Glu Lys Lys Val Lys Leu Phe
 35 40 45

Tyr Ala Gly Lys Arg Leu Lys Asp Lys Lys Ala Ser Leu Ser Lys Leu
 50 55 60

Gly Leu Lys Asn His Ser Lys Ile Leu Cys Ile Arg Pro His Lys Gln
 65 70 75 80

Gln Arg Gly Ser Lys Glu Lys Asp Thr Val Glu Pro Ala Pro Lys Ala
 85 90 95

Glu Ala Glu Asn Pro Val Phe Ser Arg Ile Ser Gly Glu Ile Lys Ala
 100 105 110

Ile Asp Gln Tyr Val Asp Lys Glu Leu Ser Pro Met Tyr Asp Asn Tyr
 115 120 125

Val Asn Lys Pro Ser Asn Asp Pro Lys Gln Lys Asn Lys Gln Lys Leu
 130 135 140

Met Ile Ser Glu Leu Leu Leu Gln Gln Leu Leu Lys Leu Asp Gly Val
 145 150 155 160

Asp Val Leu Gly Ser Glu Lys Leu Arg Phe Glu Arg Lys Gln Leu Val
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 Ser Leu Ala Val Leu Ser Val Thr Val Leu Ile Ser Ala Leu Leu Lys
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aag aga gct act gaa acc gaa gat att gtc gtt gtt cat tac gat ggc 144
 Lys Arg Ala Thr Glu Thr Glu Asp Ile Val Val Val His Tyr Asp Gly
 35 40 45

gaa aag ttg aat ttt gtg ttg cga caa cca agg ctg aat atg gtt tct 192
 Glu Lys Leu Asn Phe Val Leu Arg Gln Pro Arg Leu Asn Met Val Ser
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tac act agt ttt ctt cgt cgc gtg tgc aac gca ttt tca gta atg ccc 240
 Tyr Thr Ser Phe Leu Arg Arg Val Cys Asn Ala Phe Ser Val Met Pro
 65 70 75 80

gac aaa gcg tct ctc aag tta aac ggg gtg acc ctc aag gat ggt tca 288
 Asp Lys Ala Ser Leu Lys Leu Asn Gly Val Thr Leu Lys Asp Gly Ser
 85 90 95

ctt tcc gac caa aat gtg caa aat gga agt gaa tta gag ctc gaa tta 336
 Leu Ser Asp Gln Asn Val Gln Asn Gly Ser Glu Leu Glu Leu Glu Leu
 100 105 110

ccc aaa ctg agc ccg gca atg caa caa att gaa gca tat ata gat gag 384
 Pro Lys Leu Ser Pro Ala Met Gln Gln Ile Glu Ala Tyr Ile Asp Glu

115	120	125	
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Leu Gln Gln Asp Leu Val Pro Lys Ile Glu Ala Phe Cys Gln Ser Ser			
130	135	140	
ccc gct tcg gca caa gat gtt caa gat ttg cat aca cgc ctt agt gaa			480
Pro Ala Ser Ala Gln Asp Val Gln Asp Leu His Thr Arg Leu Ser Glu			
145	150	155	160
aca ttg ttg gct agg atg ata aaa tta gat gct gtt aat gtt gaa gac			528
Thr Leu Leu Ala Arg Met Ile Lys Leu Asp Ala Val Asn Val Glu Asp			
165	170	175	
gac cca gaa gct cgt ctt aaa aga aaa gaa gct att cgt tta tct caa			576
Asp Pro Glu Ala Arg Leu Lys Arg Lys Glu Ala Ile Arg Leu Ser Gln			
180	185	190	
caa tat ttg agt aaa cta gat tcc acc aag aat caa aac aaa tga			621
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35 40 45

Glu Lys Leu Asn Phe Val Leu Arg Gln Pro Arg Leu Asn Met Val Ser
50 55 60

Tyr Thr Ser Phe Leu Arg Arg Val Cys Asn Ala Phe Ser Val Met Pro
65 70 75 80

Asp Lys Ala Ser Leu Lys Leu Asn Gly Val Thr Leu Lys Asp Gly Ser
85 90 95

Leu Ser Asp Gln Asn Val Gln Asn Gly Ser Glu Leu Glu Leu Glu Leu

100	105	110
Pro Lys Leu Ser Pro Ala Met Gln Gln Ile Glu Ala Tyr Ile Asp Glu		
115	120	125
Leu Gln Gln Asp Leu Val Pro Lys Ile Glu Ala Phe Cys Gln Ser Ser		
130	135	140
Pro Ala Ser Ala Gln Asp Val Gln Asp Leu His Thr Arg Leu Ser Glu		
145	150	155
Thr Leu Leu Ala Arg Met Ile Lys Leu Asp Ala Val Asn Val Glu Asp		
165	170	175
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180	185	190
Gln Tyr Leu Ser Lys Leu Asp Ser Thr Lys Asn Gln Asn Lys		
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<212> DNA

<213> Homo sapiens

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atttcagac acttccaccc ctctctggcc acgtcacccc cgcctttaat tcataaaggt 180

gcccggcgcc ggcttcccgg acacgtcggc ggcgagagg ggcccacggc ggcggcccgg 240

ccagagactc ggcgcccgga gccagcgccc cgcacccgcg cccagcggg cagaccccaa 300

cccagc atg agc gcc gcc acc cac tcg ccc atg atg cag gtg gcg tcc 348

Met Ser Ala Ala Thr His Ser Pro Met Met Gln Val Ala Ser

1

5

10

ggc aac ggt gac cgc gac cct ttg ccc ccc gga tgg gag atc aag atc 396

Gly Asn Gly Asp Arg Asp Pro Leu Pro Pro Gly Trp Glu Ile Lys Ile

15

20

25

30

gac ccg cag acc ggc tgg ccc ttc ttc gtg gac cac aac agc cgc acc 444
 Asp Pro Gln Thr Gly Trp Pro Phe Phe Val Asp His Asn Ser Arg Thr
 35 40 45

act acg tgg aac gac ccg cgc gtg ccc tct gag ggc ccc aag gag act 492
 Thr Thr Trp Asn Asp Pro Arg Val Pro Ser Glu Gly Pro Lys Glu Thr
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cca tcc tct gcc aat ggc cct tcc cgg gag ggc tct agg ctg ccg cct 540
 Pro Ser Ser Ala Asn Gly Pro Ser Arg Glu Gly Ser Arg Leu Pro Pro
 65 70 75

gct agg gaa ggc cac cct gtg tac ccc cag ctc cga cca ggc tac att 588
 Ala Arg Glu Gly His Pro Val Tyr Pro Gln Leu Arg Pro Gly Tyr Ile
 80 85 90

ccc att cct gtg ctc cat gaa ggc gct gag aac cgg cag gtg cac cct 636
 Pro Ile Pro Val Leu His Glu Gly Ala Glu Asn Arg Gln Val His Pro
 95 100 105 110

ttc cat gtc tat ccc cag cct ggg atg cag cga ttc cga act gag gcg 684
 Phe His Val Tyr Pro Gln Pro Gly Met Gln Arg Phe Arg Thr Glu Ala
 115 120 125

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 Ala Ala Ala Ala Pro Gln Arg Ser Gln Ser Pro Leu Arg Gly Met Pro
 130 135 140

gaa acc act cag cca gat aaa cag tgt gga cag gtg gca gcg gcg gcg 780
 Glu Thr Thr Gln Pro Asp Lys Gln Cys Gly Gln Val Ala Ala Ala Ala
 145 150 155

gca gcc cag ccc cca gcc tcc cac gga cct gag cgg tcc cag tct cca 828
 Ala Ala Gln Pro Pro Ala Ser His Gly Pro Glu Arg Ser Gln Ser Pro
 160 165 170

gct gcc tct gac tgc tca tcc tca tcc tcc tcg gcc agc ctg cct tcc 876
 Ala Ala Ser Asp Cys Ser Ser Ser Ser Ser Ser Ala Ser Leu Pro Ser
 175 180 185 190

tcc ggc agg agc agc ctg ggc agt cac cag ctc ccg cgg ggg tac atc 924
 Ser Gly Arg Ser Ser Leu Gly Ser His Gln Leu Pro Arg Gly Tyr Ile
 195 200 205

tcc att ccg gtg ata cac gag cag aac gtt acc cgg cca gca gcc cag 972
 Ser Ile Pro Val Ile His Glu Gln Asn Val Thr Arg Pro Ala Ala Gln
 210 215 220

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Pro Ser Phe His Lys Ala Gln Lys Thr His Tyr Pro Ala Gln Arg Gly
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gag tac cag acc cac cag cct gtg tac cac aag atc cag ggg gat gac      1068
Glu Tyr Gln Thr His Gln Pro Val Tyr His Lys Ile Gln Gly Asp Asp
      240                      245                      250

tgg gag ccc cgg ccc ctg cgg gcg gca tcc ccg ttc agg tca tct gtc      1116
Trp Glu Pro Arg Pro Leu Arg Ala Ala Ser Pro Phe Arg Ser Ser Val
      255                      260                      265                      270

cag ggt gca tcg agc cgg gag ggc tca cca gcc agg agc agc acg cca      1164
Gln Gly Ala Ser Ser Arg Glu Gly Ser Pro Ala Arg Ser Ser Thr Pro
      275                      280                      285

ctc cac tcc ccc tcg ccc atc cgt gtg cac acc gtg gtc gac agg cct      1212
Leu His Ser Pro Ser Pro Ile Arg Val His Thr Val Val Asp Arg Pro
      290                      295                      300

cag cag ccc atg acc cat cga gaa act gca cct gtt tcc cag cct gaa      1260
Gln Gln Pro Met Thr His Arg Glu Thr Ala Pro Val Ser Gln Pro Glu
      305                      310                      315

aac aaa cca gaa agt aag cca ggc cca gtt gga cca gaa ctc cct cct      1308
Asn Lys Pro Glu Ser Lys Pro Gly Pro Val Gly Pro Glu Leu Pro Pro
      320                      325                      330

gga cac atc cca att caa gtg atc cgc aaa gag gtg gat tct aaa cct      1356
Gly His Ile Pro Ile Gln Val Ile Arg Lys Glu Val Asp Ser Lys Pro
      335                      340                      345                      350

gtt tcc cag aag ccc cca cct ccc tct gag aag gta gag gtg aaa gtt      1404
Val Ser Gln Lys Pro Pro Pro Pro Ser Glu Lys Val Glu Val Lys Val
      355                      360                      365

ccc cct gct cca gtt cct tgt cct cct ccc agc cct ggc cct tct gct      1452
Pro Pro Ala Pro Val Pro Cys Pro Pro Pro Pro Ser Pro Gly Pro Ser Ala
      370                      375                      380

gtc ccc tct tcc ccc aag agt gtg gct aca gaa gag agg gca gcc ccc      1500
Val Pro Ser Ser Pro Lys Ser Val Ala Thr Glu Glu Arg Ala Ala Pro
      385                      390                      395

agc act gcc cct gca gaa gct aca cct cca aaa cca gga gaa gcc gag      1548
Ser Thr Ala Pro Ala Glu Ala Thr Pro Pro Lys Pro Gly Glu Ala Glu
      400                      405                      410

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gct ccc cca aaa cat cca gga gtg ctg aaa gtg gaa gcc atc ctg gag 1596
 Ala Pro Pro Lys His Pro Gly Val Leu Lys Val Glu Ala Ile Leu Glu
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aag gtg cag ggg ctg gag cag gct gta gac aac ttt gaa ggc aag aag 1644
 Lys Val Gln Gly Leu Glu Gln Ala Val Asp Asn Phe Glu Gly Lys Lys
 435 440 445

act gac aaa aag tac ctg atg atc gaa gag tat ttg acc aaa gag ctg 1692
 Thr Asp Lys Lys Tyr Leu Met Ile Glu Glu Tyr Leu Thr Lys Glu Leu
 450 455 460

ctg gcc ctg gat tca gtg gac ccc gag gga cga gcc gat gtg cgt cag 1740
 Leu Ala Leu Asp Ser Val Asp Pro Glu Gly Arg Ala Asp Val Arg Gln
 465 470 475

gcc agg aga gac ggt gtc agg aag gtt cag acc atc ttg gaa aaa ctt 1788
 Ala Arg Arg Asp Gly Val Arg Lys Val Gln Thr Ile Leu Glu Lys Leu
 480 485 490

gaa cag aaa gcc att gat gtc cca ggt caa gtc cag gtc tat gaa ctc 1836
 Glu Gln Lys Ala Ile Asp Val Pro Gly Gln Val Gln Val Tyr Glu Leu
 495 500 505 510

cag ccc agc aac ctt gaa gca gat cag cca ctg cag gca atc atg gag 1884
 Gln Pro Ser Asn Leu Glu Ala Asp Gln Pro Leu Gln Ala Ile Met Glu
 515 520 525

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 Met Gly Ala Val Ala Ala Asp Lys Gly Lys Lys Asn Ala Gly Asn Ala
 530 535 540

gaa gat ccc cac aca gaa acc cag cag cca gaa gcc aca gca gca gcg 1980
 Glu Asp Pro His Thr Glu Thr Gln Gln Pro Glu Ala Thr Ala Ala Ala
 545 550 555

act tca aac ccc agc agc atg aca gac acc cct ggt aac cca gca gca 2028
 Thr Ser Asn Pro Ser Ser Met Thr Asp Thr Pro Gly Asn Pro Ala Ala
 560 565 570

ccg tag cctctgccct gtaaaaatca gactcggaac cgatgtgtgc tttagggaat 2084
 Pro
 575

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<211> 575

<212> PRT

<213> Homo sapiens

<400> 20

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Gln	Thr	Gly	Trp	Pro	Phe	Phe	Val	Asp	His	Asn	Ser	Arg	Thr	Thr	Thr
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Trp	Asn	Asp	Pro	Arg	Val	Pro	Ser	Glu	Gly	Pro	Lys	Glu	Thr	Pro	Ser
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Ser	Ala	Asn	Gly	Pro	Ser	Arg	Glu	Gly	Ser	Arg	Leu	Pro	Pro	Ala	Arg
65					70				75						80

Glu	Gly	His	Pro	Val	Tyr	Pro	Gln	Leu	Arg	Pro	Gly	Tyr	Ile	Pro	Ile
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Pro	Val	Leu	His	Glu	Gly	Ala	Glu	Asn	Arg	Gln	Val	His	Pro	Phe	His
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Val	Tyr	Pro	Gln	Pro	Gly	Met	Gln	Arg	Phe	Arg	Thr	Glu	Ala	Ala	Ala
	115						120					125			

Ala	Ala	Pro	Gln	Arg	Ser	Gln	Ser	Pro	Leu	Arg	Gly	Met	Pro	Glu	Thr
	130					135					140				

Thr	Gln	Pro	Asp	Lys	Gln	Cys	Gly	Gln	Val	Ala	Ala	Ala	Ala	Ala	Ala
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145		150		155		160									
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Arg	Ser	Ser	Leu	Gly	Ser	His	Gln	Leu	Pro	Arg	Gly	Tyr	Ile	Ser	Ile
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Pro	Val	Ile	His	Glu	Gln	Asn	Val	Thr	Arg	Pro	Ala	Ala	Gln	Pro	Ser
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Phe	His	Lys	Ala	Gln	Lys	Thr	His	Tyr	Pro	Ala	Gln	Arg	Gly	Glu	Tyr
225					230				235					240	
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Ser	Pro	Ser	Pro	Ile	Arg	Val	His	Thr	Val	Val	Asp	Arg	Pro	Gln	Gln
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Pro	Glu	Ser	Lys	Pro	Gly	Pro	Val	Gly	Pro	Glu	Leu	Pro	Pro	Gly	His
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			355				360					365			
Ala	Pro	Val	Pro	Cys	Pro	Pro	Pro	Ser	Pro	Gly	Pro	Ser	Ala	Val	Pro
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Ser	Ser	Pro	Lys	Ser	Val	Ala	Thr	Glu	Glu	Arg	Ala	Ala	Pro	Ser	Thr
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	405		410		415
Pro Lys His	Pro Gly Val	Leu Lys Val	Glu Ala Ile	Leu Glu Lys	Val
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Gln Gly Leu	Glu Gln Ala	Val Asp Asn	Phe Glu Gly	Lys Lys Thr	Asp
	435		440		445
Lys Lys Tyr	Leu Met Ile	Glu Glu Tyr	Leu Thr Lys	Glu Leu Leu	Ala
	450		455		460
Leu Asp Ser	Val Asp Pro	Glu Gly Arg	Ala Asp Val	Arg Gln Ala	Arg
465		470		475	480
Arg Asp Gly	Val Arg Lys	Val Gln Thr	Ile Leu Glu	Lys Leu Glu	Gln
	485		490		495
Lys Ala Ile	Asp Val Pro	Gly Gln Val	Gln Val Tyr	Glu Leu Gln	Pro
	500		505		510
Ser Asn Leu	Glu Ala Asp	Gln Pro Leu	Gln Ala Ile	Met Glu Met	Gly
	515		520		525
Ala Val Ala	Ala Asp Lys	Gly Lys Lys	Asn Ala Gly	Asn Ala Glu	Asp
	530		535		540
Pro His Thr	Glu Thr Gln	Gln Pro Glu	Ala Thr Ala	Ala Ala Thr	Ser
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<212> DNA

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<220>

<221> CDS

<222> (43)..(1416)

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Tyr	Gly	Pro	Gly	Gly	Gly	Asp	Val	Pro	Val	His	Pro	Pro	Pro	Pro	Leu	
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Tyr	Pro	Leu	Arg	Pro	Glu	Pro	Pro	Gln	Pro	Pro	Ile	Ser	Trp	Arg	Val	
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Arg	Gly	Gly	Gly	Pro	Ala	Glu	Thr	Thr	Trp	Leu	Gly	Glu	Gly	Gly	Gly	
		55					60					65				
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Gly	Asp	Gly	Tyr	Tyr	Pro	Ser	Gly	Gly	Ala	Trp	Pro	Glu	Pro	Gly	Arg	
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gcc	gga	gga	agc	cac	cag	gag	cag	cca	cca	tat	cct	agc	tac	aat	tct	342
Ala	Gly	Gly	Ser	His	Gln	Glu	Gln	Pro	Pro	Tyr	Pro	Ser	Tyr	Asn	Ser	
	85				90					95					100	
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Asn	Tyr	Trp	Asn	Ser	Thr	Ala	Arg	Ser	Arg	Ala	Pro	Tyr	Pro	Ser	Thr	
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Tyr	Pro	Val	Arg	Pro	Glu	Leu	Gln	Gly	Gln	Ser	Leu	Asn	Ser	Tyr	Thr	
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Asn	Gly	Ala	Tyr	Gly	Pro	Thr	Tyr	Pro	Pro	Gly	Pro	Gly	Ala	Asn	Thr	
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gcc	tca	tac	tca	ggg	gct	tat	tat	gca	cct	ggt	tat	act	cag	acc	agt	534
Ala	Ser	Tyr	Ser	Gly	Ala	Tyr	Tyr	Ala	Pro	Gly	Tyr	Thr	Gln	Thr	Ser	
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Tyr	Ser	Thr	Glu	Val	Pro	Ser	Thr	Tyr	Arg	Ser	Ser	Gly	Asn	Ser	Pro	
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Ala	Pro	Pro	Leu	Arg	Gly	Gln	Val	Pro	Gly	Tyr	Pro	Pro	Ser	Gln	Asn		
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Pro	Gly	Met	Thr	Leu	Pro	His	Tyr	Pro	Tyr	Gly	Asp	Gly	Asn	Arg	Ser		
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Val	Pro	Gln	Ser	Gly	Pro	Thr	Val	Arg	Pro	Gln	Glu	Asp	Ala	Trp	Ala		
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Gln	Gln	Pro	Lys	Asp	Ser	Ser	Tyr	Pro	Tyr	Ser	Gln	Ser	Asp	Gln	Ser		
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Met	Asn	Arg	His	Asn	Phe	Pro	Cys	Ser	Val	His	Gln	Tyr	Glu	Ser	Ser		
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Gly	Thr	Val	Ile	Asn	Glu	Asp	Ser	Asp	Leu	Leu	Asp	Ser	Gln	Val	Gln		
325					330				335						340		
tat	agt	gct	gag	cct	cag	ctg	tat	ggt	aat	gcc	acc	agt	gac	cat	ccc	1110	
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Ser Gly Leu Ser Asp Asp Lys Asn Tyr Lys Lys Leu Glu Arg Ile Leu
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/21053

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : 07N 21/02; C07K 1/00

US CL : 530/387.1, 350; 435/6, 7/1; 536/23.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/387.1, 350; 435/6, 7/1; 536/23.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,652,223 A (KOHN ET AL) 29 July 1997(29/7/97) see entire document.	2-5, 14, 32-34
X	Database Genbank-EST, National Center for Biotech. Info., Accession No. AA693697, HILLIER, L. ET AL. 'WashU-NCI human EST Project,' 16 December 1997, see entire reference.	2
X	Database Genbank-EST, National Center for Biotech. Info., Accession No. AA456862, NCI_CGAP, 'National Cancer Institute, Cancer Genome Anatomy Project (CGAP), Tumor Gene Index,' 15 August 1997, see entire reference.	2,4



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

24 NOVEMBER 1999

Date of mailing of the international search report

19 JAN 2000

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

SHEELA J. HUFF

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No
PCT/US99/21053**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1, 13, 24, 25
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

No meaningful search could be carried out because no limitations could be placed on the sequence
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest☐

The additional search fees were accompanied by the applicant's protest

☐

No protest accompanied the payment of additional search fees

INTERNATIONAL SEARCH REPORT

International application No
PCT/US99/21053

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database Genbank, National Center for Biotech. Info., Accession No. G29287, MYERS, R.M., 04 October 1996, see entire reference.	2,4
X	Database Genbank, National Center for Biotech. Info., Accession No. G06974, HUDSON, T., "Whitehead Institute.MIT Center for Genome Research,'19 October 1995, see entire reference.	2,4
X	Database Genseq, Derwent, Alexandria, Virginia, Accession No. V81267, OTSUKA PHARM CO LTD, 'New Bcl-2 interaction prrtein gene (Bis)- useful for elucidation of the molecular mechanism of apoptosis, and in diagnosis, prevention and treatment of diseases,' 15 December 1998 see enire reference.	2-5
X	Database, Geneseq, Derwent, Alexandria, Virginia, Accession No. T19051, MATSUBARA ET AL., "Identifying gene signatures in 3'-directed human cDNA library,' 01 June 1995, see entire reference.	2,4
X	Database Geneseq, Derwent, Alexandria, Virginia, Accession No. Q90296, LA JOLLA CANCER RES FOUN. 'Human Bcl-2-associated protein BAG-1 cDNA,'18 May 1995 see entire reference.	2-5,14